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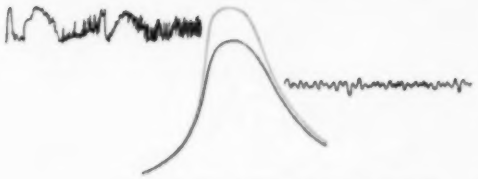

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1. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Livingston, S., and Petersen, D.: To be published.
3. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

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SECTION ON
NEUROLOGY

Diabetic Ophthalmoplegia

Report of Case, with Postmortem Study and Comments on Vascular Supply of Human Oculomotor Nerve

PIERRE M. DREYFUS, M.D.; SALOMON HAKIM, M.D., and RAYMOND D. ADAMS, M.D., Boston

I. Introduction

Paralysis of the third, fourth, or sixth cranial nerve as a complication of diabetes mellitus was first recognized as a clinical entity by Ogle in 1866.[1] Since that time, numerous, detailed clinical descriptions of cases of ocular palsy in diabetic patients have appeared in the medical literature. As many writers have observed, the ophthalmoplegia is often seen in patients who have had mild diabetes of long standing, frequently complicated by retinopathy, nephropathy, peripheral neuropathy, and lenticular opacities. The third and sixth cranial nerves are the ones most frequently affected, the paralysis coming on rapidly, sometimes in a matter of hours, and clearing up completely within a few weeks or months. The ophthalmoplegia is frequently accompanied by pain, often severe, which is localized within or behind the orbit in a distribution which may correspond to the ophthalmic division of the trigeminal nerve. When the third nerve is affected, pupillary function often remains undisturbed.[2-7] One or both eyes may be affected, usually in succession.

The pathology of this condition, which has never hitherto been reported, has remained a subject of much speculation. A metabolic lesion, inflammation, or arterial disease with ischemic degeneration of the nerve, an infarction or hemorrhage in the nucleus or in the intramedullary parts of the nerve have all been postulated at one time or other. Our case report contains what we believe to be the first description of the morbid anatomy of this disease; and, although failing to provide a complete solution to its cause and pathogenesis, it does account for many of the puzzling features of the disease.

II. Clinical Data

The patient, a 62-year-old white housewife, was admitted to the hospital on March 22, 1955, because of ptosis of the left eyelid and a left frontal headache.

She was known to have had diabetes mellitus for about 10 years and was receiving 10 units of isophane insulin (NPH Insulin) daily. Her diet was not strict, and her diabetes was probably poorly regulated. She had had two insulin reactions, one 10 years and the other 8 months prior to her admission. These reactions consisted of fainting spells lasting about 15 minutes, which were promptly relieved by the ingestion of orange juice. For about 10 years prior to her admission she had complained of what she termed "chronic circulatory trouble" of her feet, characterized by

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This paper was presented in part at the 81st Annual Meeting of the American Neurological Association, on June 19, 1956, in Atlantic City.

From the Neurology Service and Department of Pathology of the Massachusetts General Hospital, and the Department of Neuropathology, Harvard Medical School. This study was supported in part by a grant from the Harrington Fund.

cold, swollen, sweaty toes. She denied having had the symptoms of intermittent claudication. Her past and family histories were otherwise unremarkable.

The illness which brought the patient to the hospital began five weeks prior to her admission, with an upper respiratory infection consisting of a "stuffy" nose, a nasal discharge, and a mild left frontal headache. She visited an ice-skating show, which appeared to cause a worsening of her symptoms. The next day she noted double vision, which was present in all directions of gaze, and four days later she discovered that she could not open her left eye. The ptosis was accompanied by a sharp, "knife-like" pain in the left frontal and temporal region with radiation into the orbit and toward the occiput. With lessening severity, headache persisted for the next month, in fact, until two days before admission to the hospital; and she was of the opinion that there had been no change in the ocular palsy. The patient complained of no other neurological symptoms.

The general physical examination on admission showed the patient to be a moderately obese, elderly woman in no acute distress. Her pulse was 88 per minute; her respirations 22 per minute, and her blood pressure 180/100 mm. Her heart was slightly enlarged to percussion. Both femoral pulses were weak to palpation; the popliteal pulses could not be felt. The posterior tibial pulses were extremely weak, and no dorsalis pedis pulse could be felt. No other abnormality was detected.

The neurological examination revealed a normal mental status. Examination of the cranial nerves disclosed ptosis of the left eyelid, almost complete; and when the lid was lifted, the globe was found to be turned laterally in a position of partial abduction. It could not be adducted beyond the midline, and only the slightest degree of elevation and depression was possible. On attempted downward gaze, minimal intorsion was observed, indicating integrity of the trochlear nerve. The movements of the right eye were normal. The pupils were nearly equal in size, the left being 3.5 mm. in diameter and the right 3 mm.; both reacted to light, although somewhat sluggishly, and in accommodation. With the exophthalmometer, a slight prominence of the left eye was demonstrated. Visual acuity was 20/50, O. D., and 20/70, O. S., with full visual fields. Ophthalmoscopic examination showed a few scattered punctate hemorrhagic areas, the berry aneurysms of diabetes; and there were also patches of white exudate in both eyes. There was no papilledema. Sensation over the face was normal, and the corneal reflex was intact. The only other neurological abnormalities were a symmetrical distal hypesthesia and hypalgesia in the toes of both feet and absence of ankle jerks. Both plantar reflexes were flexor.

Laboratory Examinations.—The hemoglobin, white cell count, and differential count were normal. The urine had a specific gravity of 1.016; it contained 3+ albumin, and 2+ sugar, and 10 white cells, 3 red cells, and rare hyaline casts per high-power field. The sedimentation rate was 34 mm. in one hour. Both Hinton and Wassermann reactions were negative. A fasting blood sugar determination was 221 mg. per 100 cc.; the nonprotein nitrogen was 42 mg. per 100 cc. A lumbar puncture showed an initial pressure of 160 mm. of water, no cells, a total protein of 72 mg. per 100 cc., and a normal colloidal gold curve. An electroencephalogram was normal. X-rays of the skull and chest were negative.

In order to rule out an aneurysm of the internal carotid artery, an open-type left carotid arteriogram with colloidal thorium dioxide (Thorotrast) was done under thiopental (Pentothal) sodium anesthesia. No vascular abnormality was seen on the x-rays. Shortly after the procedure the patient developed dysphagia with swelling and pain around the site of operation. The following day the dysphagia became severer, and she developed slight respiratory stridor. She could not swallow fluids. Her color and respiratory rate were normal. Later that day she suddenly became acutely dyspneic and cyanotic, and within a few minutes cardiac arrest occurred. All attempts at resuscitation failed.

III. Pathological Findings

A. General Pathology.—Autopsy was performed 17 hours after death.

Examination of the larynx, trachea, and upper esophagus revealed edema and hemorrhagic infiltration. The operative site in the left side of the neck was markedly hemorrhagic. The hemorrhage extended into the retromanubrial space.

The lungs showed mild pulmonary edema of both lower lobes. The heart weighed 400 gm. and revealed no gross pathology. The coronary arteries and the aorta contained segments of calcification and sclerotic plaques on the intima.

Microscopic examination of the kidneys demonstrated glomeruli in varying stages of fibrosis and hyalinization. Small ovoids of hyaline material could be seen in a few glomeruli. Some of the renal tubules showed a thick, brightly hyalinized basement membrane, located near fibrosed glomeruli. A few tubules contained bright, eosinophilic, colloid-like material. These changes were regarded as representing intercapillary glomerulosclerosis (Kimmelstiel-Wilson disease). Microscopic sections of the pancreas revealed rare hyalinized islets of Langerhans and arteries with thickened walls and nearly occluded lumina. The

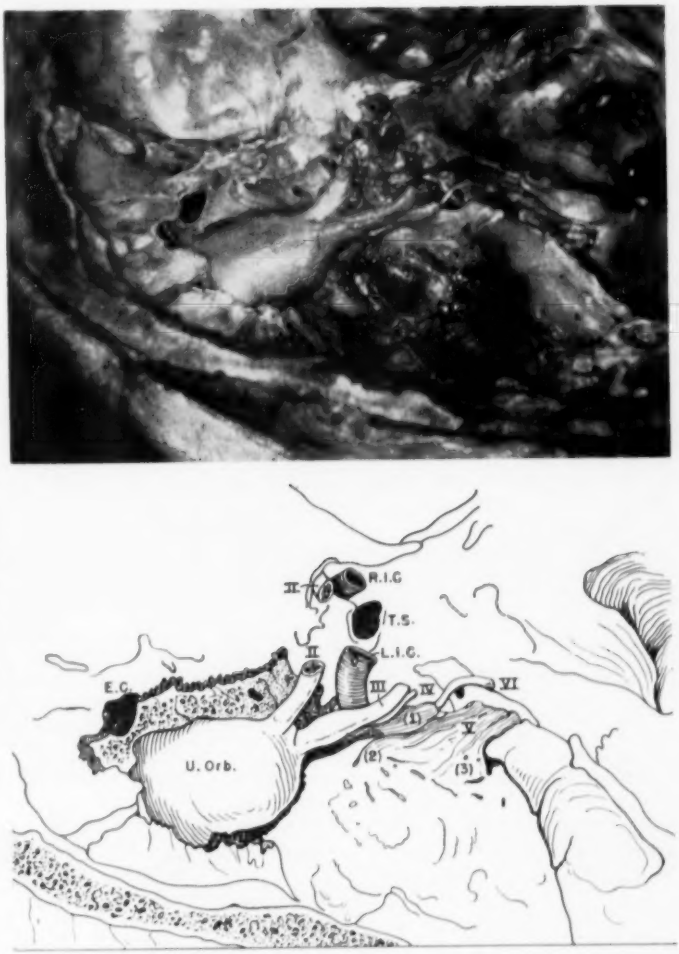


Fig. 1.—Gross photograph and illustrative diagram of unroofed orbit and perisellar region of the skull. The cavernous sinus is dissected to show the swollen third nerve and other cranial nerves. *U. Orb.*, unroofed orbit; *II*, left and right optic nerves; *III*, left oculomotor nerve; *IV*, left trochlear nerve; *V*, left Gasserian ganglion with (*1*) ophthalmic branch, (*2*) maxillary branch, (*3*) mandibular branch; *VI*, left abducens nerve; *L. I. C.*, left internal carotid artery; *R. I. C.*, right internal carotid artery; *T. S.*, sella turcica; *E. C.*, ethmoid cell.

thyroid was involved by a mild chronic nonspecific thyroiditis.

A sagittal section through the left eye showed the vitreous to contain aggregates of small vessels in a connective tissue meshwork attached to the walls of retinal veins. This condition appeared to be typical of retinitis proliferans. In the small and medium-sized arteries of the retina and choroid there were marked narrowing of the lumen and thickening of the vessel wall. A flat mount of the right retina stained with the Hotchkiss method revealed numerous small, thin-walled aneurysmal dilatations of the retinal veins.

B. Neuropathology.—1. Gross Findings: The brain weighed 1180 gm. There was moderate atherosclerosis of the arteries supplying the brain, but no other vascular abnormality or aneurysmal dilatation could be found. Superficially the cerebrum, brain stem, and cerebellum appeared entirely normal.

After removal of the brain, the right and left third, fourth, and sixth cranial nerves within the subarachnoid space were examined, and no abnormalities were found. A dissection of all the nerves innervating the extraocular muscles of both eyes, the Gasserian ganglia, and the ophthalmic division of the trigeminal nerves was carried out from a point where these structures pierced the dura mater, on through the cavernous sinus to their points of termination within the orbit. The left internal carotid artery and its siphon were inspected within the cavernous sinus, and no occlusion or aneurysmal dilatation was seen; the artery was moderately atherosclerotic. The distal

two-thirds of the intracavernous portion of the left third nerve was seen to be greatly swollen, being thickened to about twice its normal size. This swelling also involved the oculomotor nerve at a point immediately behind the superior orbital fissure, where it reached a diameter approximating that of the optic nerve (Fig. 1). The intraorbital portion of the third nerve and its branches appeared normal. The left fourth and sixth cranial nerves, as well as all of the cranial nerves on the right side, the extraocular muscles, and the ciliary ganglion, were of natural appearance.

After formalin fixation, coronal sections were made through the cerebral hemispheres, brain stem and cerebellum, but no gross lesions were observed. The spinal cord and peripheral nerves were not examined.

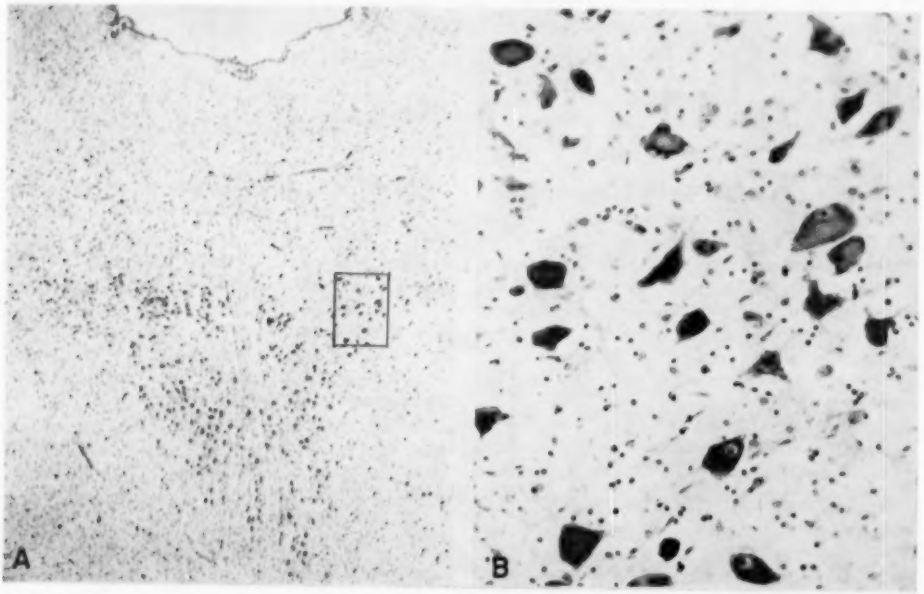
2. Microscopic Findings: Representative sections of the brain, brain stem, and cerebellum stained with cresyl violet showed very few changes. A small focal lesion could be seen between the globus pallidus and the amygdaloid nuclei on the left. The lesion consisted of a cluster of fibrillary astrocytes, rare macrophages, and activated microgliacytes. No occluded vessel was found. The lesion was compatible with an old area of infarction.

In all parts of the brain the large and medium-sized arteries were seen to be involved by atherosclerosis, with intimal thickening by fibrous tissue and subintimal accumulation of fatty macrophages. Arterioles measuring between 15μ and 45μ had narrow lumens, due to intimal thickening and occasional endothelial hyperplasia. No other striking abnormalities were encountered in the brain.

Serial sections through the midbrain and the upper part of the pons at a level which included the nuclei of the third, fourth, and sixth cranial nerves were obtained for Nissl stain. No areas of infarction or hemorrhage could be found. Some of the motor cells of the principal oculomotor nucleus on the left and an occasional motor cell in a similar area on the right were rounded and exhibited an eccentricity of the nucleus, which occasionally seemed to bulge beyond the cell membrane and central chromatolysis. Even after one allowed for the normally rounded appearance of the nerve cells in the oculomotor nuclei, the contrast between the left and the right side was so marked as to leave no doubt that this change was a typical "axonal reaction" (Fig. 2). All parts of the main oculomotor nucleus on the left appeared to be affected to an equal extent. The nuclei of Edinger-Westphal and Perlia were of normal appearance, as were also the fourth and sixth nerve nuclei.

The right and the left oculomotor nerves were sectioned, embedded, and stained according to the plan outlined in the legend to Figure 3. An ab-

Fig. 2.—*A*, oculomotor nucleus in transverse section stained by Nissl technique. The plane of the section was not exactly horizontal, and the two sides are not comparable. In a series of sections, however, some of the cells within the rectangle (seen in *B*) were more rounded and chromatolytic than those on the right side. Reduced to 73% of (*A*) mag. × 125; (*B*) mag. × 450.



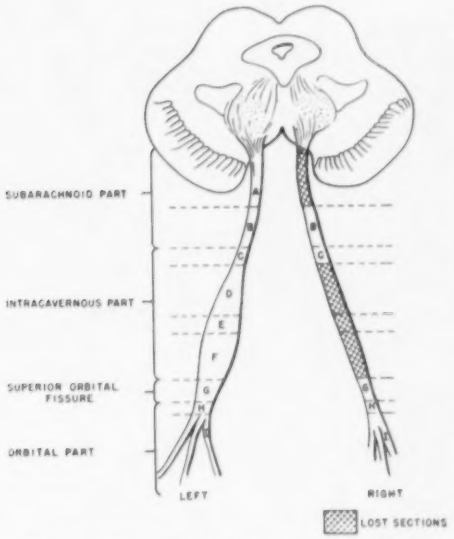


Fig. 3.—Diagram of midbrain and oculomotor nerves to show plane of microscopic examination.

Section	Embedding, Cutting, and Staining Methods Used	
	Left	Right
A	Serial cross sections (paraffin) 1. Verhoeff elastic tissue stain 2. Bodian axis-cylinder stain	Not cut
B	Serial longitudinal sections (paraffin) 1. Hematoxylin and eosin 2. Phosphotungstic acid-hematoxylin 3. Bodian stain	Same as left
C	Serial cross sections (paraffin) 1. Hematoxylin and eosin 2. Phosphotungstic acid-hematoxylin 3. Bodian stain	Same as left
D	Serial cross sections (paraffin) 1. Verhoeff elastic tissue stain 2. Bodian stain	Nerve lost
E	Serial cross sections (paraffin) 1. Hematoxylin and eosin 2. Phosphotungstic acid-hematoxylin 3. Bodian stain	Nerve lost
F	Serial longitudinal sections (paraffin) 1. Hematoxylin-eosin 2. Phosphotungstic acid-hematoxylin 3. Bodian stain	Nerve lost
G	Cross sections (frozen) 1. Oil red O 2. Spielmeyer stain	Nerve lost
H	Cross sections (paraffin) 1. Hematoxylin and eosin 2. Phosphotungstic acid-hematoxylin	Same as left
I	Longitudinal and cross sections 1. Hematoxylin and eosin 2. Phosphotungstic acid-hematoxylin	Same as left

normality of blood vessels was observed in the sections of both oculomotor nerves. It consisted of an increase in adventitial collagen with scattered perivascular lymphocytes, and an eccentric thickening and occasional hyalinization with proliferation of endothelial cells in the intima. The lumen of some of the smaller arteries and arterioles was greatly reduced, but no occlusion could be observed.

Section *A* (Fig. 3), which was the most proximal part of the nerve nearest the midbrain, appeared normal.

Section *B*, which was the subarachnoid part of the nerve, appeared normal on both sides.

Section *C*, which was the part of the nerve that lay within the cavernous sinus, was normal on the right side. The corresponding part of the left oculomotor nerve showed slight alteration of some of the nerve fibers, characterized by swelling and fragmentation of the sheaths. Also, a few of the axis cylinders were pale-staining and widened. There appeared to be a slight increase in peri- and endoneurium.

Section *D*, which was the proximal half of the intracavernous part of the left nerve, seemed more clearly to include a zone of transition between normal and abnormal nerve. Scattered large fibers, especially in the center of the nerve, showed loss and fragmentation of myelin, and a slight increase in the thickness of peri-, as well as epineurial, connective tissue was noted.

Section *E* (in serial transverse sections) and Section *F* (in serial longitudinal sections), which were from the distal half of the intracavernous part of the left third nerve, showed the site of most extensive pathology. These sections were taken through the area of maximal swelling (Fig. 4). The cross sections from *E* showed extensive destruction, with disappearance of both myelin sheaths and axis cylinders in an irregularly shaped focus, but most marked in the center of the nerve. Large and medium-sized nerve fibers in the range of 5μ-10μ were more affected than the smaller fibers, measuring 3μ or less; the latter were numerous in the periphery of the nerve. The lesion reached the surface of the nerve only in a few places, apparently in relation to several endoneurial arteries. The latter, as well as all other arteries and veins, were patent in all sections, from one end of the lesion to the other. However, some deeply pink-staining homogeneous fibrinoid material containing nuclear fragments was seen in the walls of several small, centrally placed arteries (Fig. 5). This material stained blue-purple with phosphotungstic acid-hematoxylin; it was not selectively stained by the periodic acid-Schiff method (after formalin fixation), nor did any other component of the vessels show an affinity for this stain. The nerve fascicles were separated by thick strands of connective tissue.

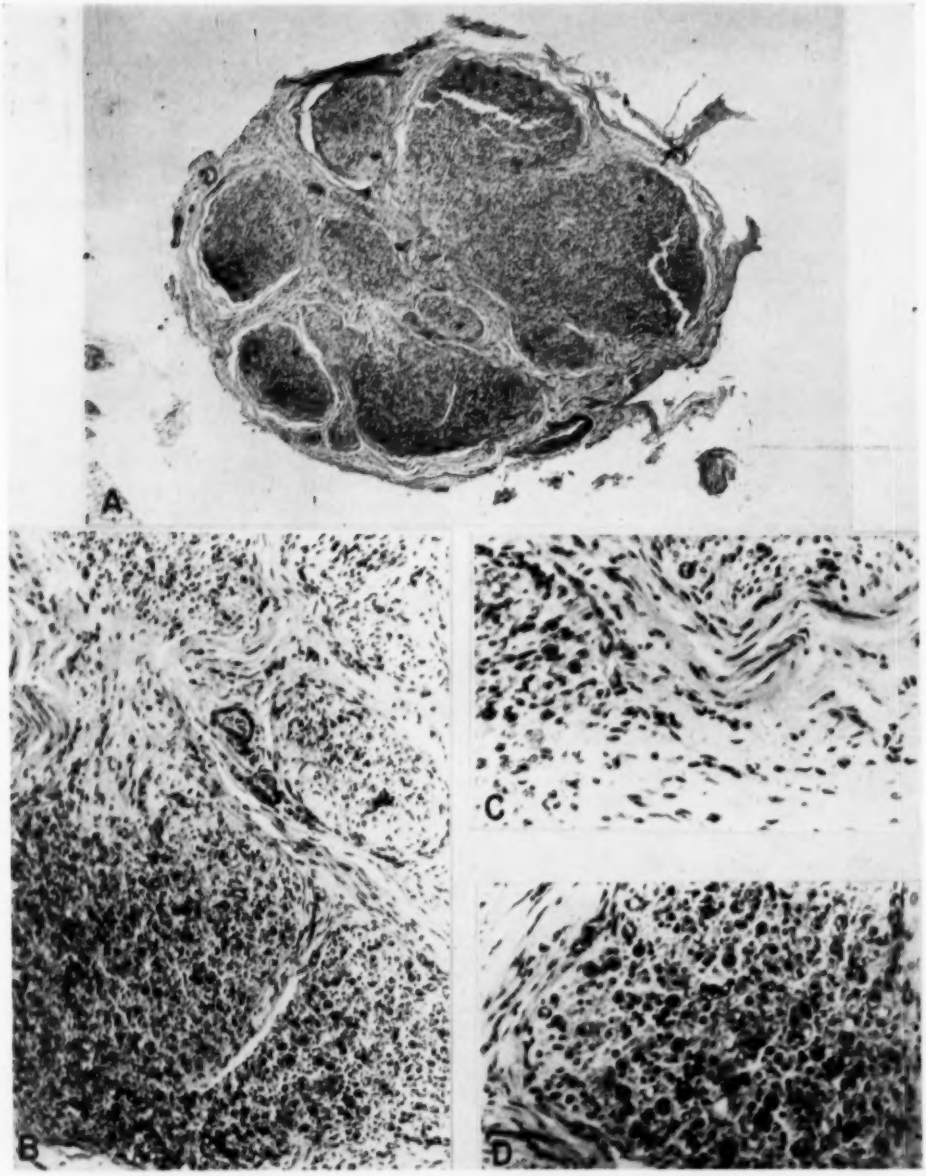


Fig. 4.—*A*, low-power cross section of the swollen part of the left oculomotor nerve. Note the relatively pale central zone with sparse medullated fibers and the more normal periphery. Heidenhain myelin stain; reduced to 88% of mag.× 37. *B*, higher magnification of the lower fascicle in *A*, identified by the curved slit, to show contrast between central part, above, and peripheral part, below; reduced to 88% of mag.× 125. *C* and *D*, still higher magnification of central part (*C*) and peripheral part (*D*); reduced to 88% of mag.× 250.

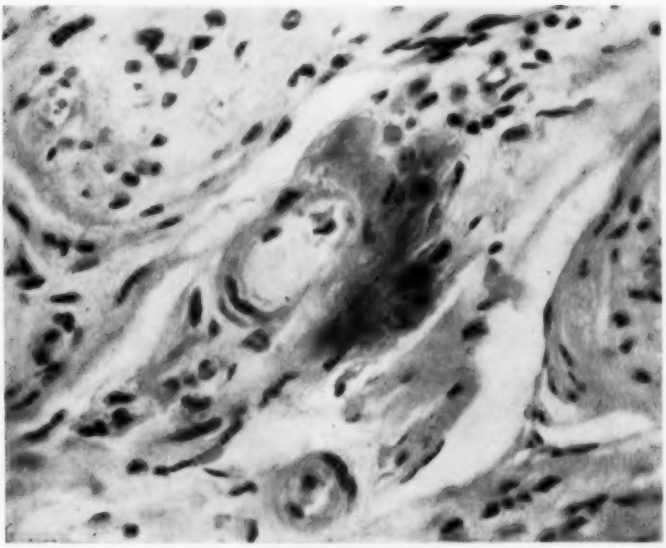


Fig. 5.—A cluster of blood vessels in the center of the swollen part of the left oculomotor nerve. The central vessel is a small artery and the deeply staining homogeneous material is an eosinophilic fibrinoid deposit in the adjacent tissue. Hematoxylin and eosin; reduced to 88% of mag. ×450.

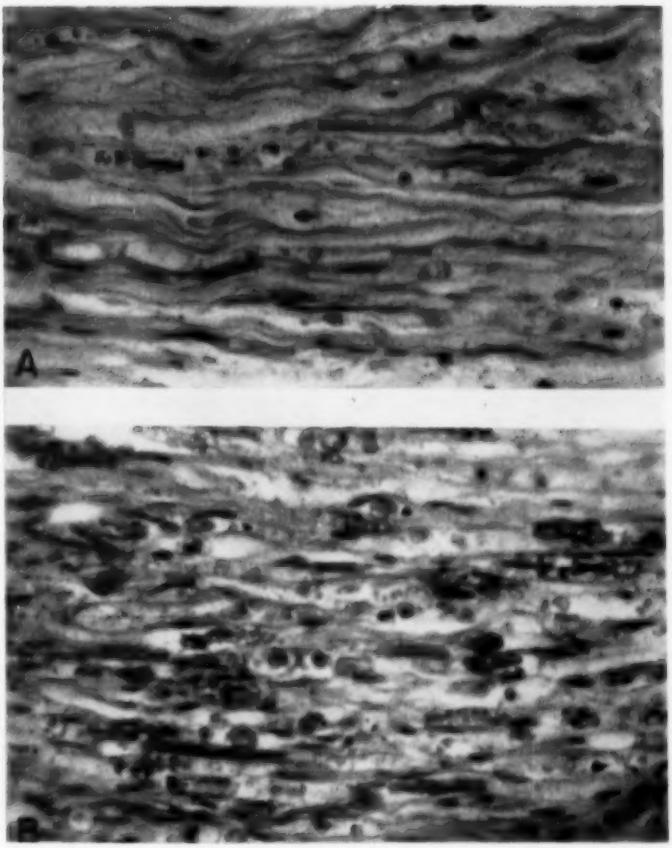


Fig. 6.—Longitudinal sections of left oculomotor nerve. Phosphotungstic acid-hematoxylin stain; ×250. *A* is from center of segment *F* and shows disappearance of nerve fibers with only a few fragments of degenerated myelin remaining in the endoneurial connective tissue. *B*, a more distal segment (*I*) and demonstrates fragmentation of myelin and ovoids, interpreted as recent Wallerian degeneration. ×340.

The longitudinal sections from Section *F* showed, in addition to disappearance of nerve fibers, other fibers which were in all stages of myelin breakdown (Fig. 6). In some, the myelin sheaths were greatly swollen, with loss of the usual herringbone arrangement; others were fragmented into large spheres or small, pale-staining granules. Ovoids and rare digestion chambers containing macrophages with ingested myelin particles and fragmented axons could be seen in all parts. The axis cylinders in these sections were very severely affected. They, too, were greatly reduced in number in the center of the nerve. Some were greatly swollen and pale-staining, while others were broken up into beads or had assumed corkscrew or serpentine shapes. In cell stains the altered tissue had a rather loose, edematous appearance. Fibroblasts appeared to be somewhat increased in the area of maximal damage. The Schwann cells had not increased significantly in number. As had been noted in the cross sections, the perineurium was greatly increased in amount and formed wide, sweeping strands, separating the nerve fascicles. This was most pronounced in the center of the nerve. The amount of endoneurial connective tissue was also increased.

In many of the sections there were longitudinally oriented strands of connective tissue admixed with delicate filaments of axoplasm. The latter had no visible myelin sheaths. Three or four such axis cylinders formed intertwining bundles, each surrounded by connective tissue sheaths. The strands of reticular connective tissue and axis cylinders maintained a parallel relationship to one another. In a few places Schwann cells had increased in number, being arranged in double parallel rows with a narrow space between them. These had the appearance of the so-called bands of Büngner. These findings were believed to represent a regenerative process.

Section *G*, which was the oculomotor nerve in the posterior part of the orbit just anterior to the superior orbital fissure and beyond the maximal extent of pathology, showed extensive and widespread myelin and axis-cylinder destruction. The myelin was fragmented, and there were a few digestion chambers containing fat-laden macrophages, which stained orange-red with the oil red O stain. Even here, however, there were numerous intact medium-sized and small fibers.

Section *H* was from the intraorbital part of the nerve prior to its final division, and it again showed widespread myelin and axis-cylinder destruction. Less connective tissue appeared to be present here than in more proximal sections; yet there was more than in the corresponding section of the right nerve, which appeared essentially normal. It was felt that the changes in Sections *G* and *H* represented those of Wallerian degeneration.

Section *I*, which included the terminal twigs of the oculomotor nerve, will be described with the extraocular muscles.

The right and left frontal nerves, the trochlear and abducent nerves on both sides, and the left ciliary ganglion and short ciliary nerves were examined microscopically. The vascular abnormality noted elsewhere was present here, but no occluded blood vessels could be seen. Otherwise these structures were believed to be normal.

The following extraocular muscles were sectioned longitudinally and crosswise, embedded in paraffin, and stained with hematoxylin and eosin, as well as with phosphotungstic acid-hematoxylin: right and left lateral recti, superior recti, superior obliques, medial recti, levatores palpebrarum superiorum, and left inferior rectus. The fiber size of these muscles averaged between 15μ and 20μ. No abnormality of muscle fibers, sarcolemmal nuclei, or fibrous tissue could be discerned. Nerve twigs in the muscles supplied by the left oculomotor nerve showed numerous nerve fibers in various stages of degeneration: There were fragmentation of myelin into balls, digestion chambers, and large macrophages containing myelin particles. This, too, was considered to represent Wallerian degeneration.

IV. Comment

This case presented a number of interesting clinical, anatomical, and pathological features which deserve further comment.

The paralysis of the ocular muscles supplied by the oculomotor nerve was remarkably complete, more so than one would have expected from observing the extent of the lesion. As a rough estimate not more than a fourth or a fifth of the nerve fibers had disappeared or were in the process of degeneration; yet all oculomotor functions except pupillary constriction, and probably ciliary muscle action, had been paralyzed for more than five weeks. Presumably the paralysis was to a large extent due to a disorder of function rather than an irreversible structural change; and this would account for the relatively rapid and complete recovery that occurs in most cases of diabetic

ophthalmoplegia, long before regeneration could have taken place. Nevertheless, regeneration was in evidence, and could eventually have resulted in improvement after a longer interval of time, a phenomenon which has been observed in some of the published cases.

The retention of pupilloconstrictor function probably had as its anatomical basis the sparing of nerve fibers in the peripheral or subepineurial part of the nerve. Many of these peripheral fibers are of small diameter, measuring about 3μ in diameter, which, according to the study of Sunderland and Hughes,[8] is about the size of the pupilloconstrictor fibers. Moreover, these authors demonstrated that the autonomic fibers are located in the periphery of the nerve, especially on its superior surface, which had escaped injury in our case. Sunderland and Hughes also made another interesting observation—that the oculomotor nerve is the only one of the ocular nerves which contains a large percentage of small fibers in its periphery. Apparently the superficial position of these fine fibers both exposes them to external pressure and protects them against the effects of ischemia.

The cause of the orbital and temporal pain, which was another prominent symptom in our case, could not be ascertained. The frontal branch of the trigeminal nerve was examined and found to be normal, but the more proximal parts of the trigeminal nerve were lost, unfortunately. It is probable that edema and swelling of the diseased segment of the oculomotor nerve irritated or compressed the sensory nerve twigs in its sheath. According to Stibbe,[9] bundles of sensory nerve fibers course along the epineurial sheath of the oculomotor nerve and join the ophthalmic division of the trigeminal nerve within the cavernous sinus. Undoubtedly a few of these fibers could be irritated without suffering sufficient damage to be manifest in microscopic sections or as a sensory loss in clinical tests.

The pathological process was remarkable in several respects. First, it had induced a fusiform enlargement of the oculomotor nerve, which on microscopic section proved to be a mixed pseudoneuroma and neuroma. Over a distance of a centimeter or more the nerve was swollen to about one and a half times its normal diameter (Figs. 1 and 4). This enlargement was not due solely to a proliferation of axons and connective tissue from the proximal end of the lesion, as in an ordinary traumatic neuroma, but was the result of edema and cellular infiltration, as well as an increase in connective tissue in the endoneurium, perineurium, and epineurium. The lesion, therefore, resembled in certain respects the pseudoneuroma described by Tinel[23] and others in their studies of nerve injuries. It was surprising that the swelling of a pseudoneuroma should persist after five weeks, but this was probably due to the vigor of the reparative processes. As shown by the experiments of Denny-Brown and Brenner,[24] there is a constantly changing microscopic pathology in pseudoneuroma. Beginning as a congestion of blood vessels, edema, and a segmental shattering of myelin sheaths, it continues for some weeks as a cellular infiltration and an edema of the interstitial tissue. Finally, it subsides unless some of the nerve fibers have been interrupted, in which case fibrosis and axonal proliferation add to the volume of the injured segment. In the latter instance a pseudoneuroma becomes a neuroma. Presumably this was taking place in our case.

The principal characteristic of the microscopic lesion was an incomplete necrosis of parenchymal and interstitial tissue. All neural elements—myelin sheaths, axis cylinders, Schwann cells, and connective tissue—were affected in the region of maximum damage; and those elements capable of proliferating, i. e., connective tissue and axons of the central stump, had begun to do so. An infiltration of macrophages and interstitial edema were also found. The transition between normal and affected nerve was relatively abrupt. The changes in the oculomotor nucleus were assumed to be of secondary or retrograde type, whereas those in the segment of nerve distal to the lesion

were typical of Wallerian degeneration. Other noteworthy features of the pathological process were overgrowth of connective tissue involving epineurium, perineurium, and, to an even greater degree, the endoneurium; an arteriosclerosis of the intraneural vessels, with a fibrinoid change in one of them, and a regeneration of axis cylinders.

In attempting to interpret these pathological changes, we were inclined to the view that they could best be explained as direct effect of and a reaction to an incomplete focal ischemia resulting from occlusion of a nutrient artery. Although other possibilities could not be absolutely excluded, there was no evidence of hemorrhagic or inflammatory disease of the nerve, and the focal nature and severity of the pathological changes were not in keeping with any known toxic or metabolic disorder. We were disappointed, however, in our failure to find an occluded artery or vein, either within or on the surface of the nerve in serial sections through the entire nerve. Nor could we demonstrate any certain relationship between the lesion and the curious deposits of material which characterize Kimmelstiel-Wilson disease and the vascular changes in diabetic retinopathy. It is true that there was one vessel within the nerve which was surrounded by an eosinophilic material, but it was very small and was shown in serial sections to be patent throughout its intraneurial course. Nonetheless, it is possible that a nutrient artery had become thrombosed at its origin from a larger artery outside the nerve, and that it had been overlooked in the postmortem examination because of our ignorance of the arterial supply of the oculomotor nerve. The demonstration of fairly severe vascular disease elsewhere would favor this explanation, and it also has the support of other studies of diabetic neuropathy, such as that of Woltman,[10] which postulate an underlying vascular disorder in at least one type of diabetic neuropathy. Moreover, the lesion itself bore a striking resemblance to what has been called "ischemic neuropathy." Lapinsky, in 1898,[11,12] was one of the first to study the lesions observed in the nerves of limbs amputated because of gangrene secondary to occlusive vascular disease. In the cases which had suffered from chronic vascular insufficiency, he observed a thickening of nerves and a marked increase in endo- and epineurium, particularly around blood vessels, with relatively slight destruction of myelin sheaths or axis cylinders. In contrast, the nerves of cases which had suffered from acute ischemia (five to eight days after the occlusion of a major vessel) showed marked degeneration of myelin sheaths and axis cylinders and some swelling and edema, but no proliferation of connective tissue. In all of the cases the occluded blood vessel had occurred outside the nerve and intraneural vessels were patent. Duhot [13] found similar changes and referred to them as *transformation cirrhotique*. Identical observations were made by Pancenko,[14] Barker,[15] and Priestley.[16]

The lesion in our case also is similar in certain respects to those seen in periarteritis nodosa, another example of an ischemic neuropathy. Kernohan and Woltman,[17] who have written on this subject, found in their series of cases areas of infarction in sciatic nerves and a marked increase in connective tissue. We have confirmed this in other cases, particularly in the central parts of the nerve. Characteristically in polyarteritis nodosa, however, many of the nutrient vessels within and on the surface of the nerve reveal inflammation and thrombosis.

Our impression that the changes which we have described in this case are indicative of ischemia seems to be shared by Krücke,[18] who feels that Wallerian degeneration and fibrosis (*ischemische Kollagenisierung*) are common denominators of the ischemic neuropathies. The sudden or acute onset and step-like progression of the ophthalmoplegia in our case, and in others very similar to it, would be best accounted for on the basis of ischemia.

Any final conclusion as to the vascular origin of this disease must, however, await more definite pathological studies and a

more complete knowledge of the blood supply and circulatory arrangements within cranial nerves.

In order to clarify our own ideas regarding the possibility of vascular occlusion and ischemic neuropathy of a cranial nerve, we reviewed a number of anatomical studies and carried out a series of dissections in humans and animals. This proved to be instructive but left us in doubt on many important points. Despite a fairly substantial number of anatomical papers on the blood supply of peripheral nerves, we found that rather little attention had been given to the cranial nerves. Certain of the anatomical principles which have been established by Sunderland[19] and Adams[20] for peripheral nerves in general may, however, apply to the oculomotor nerve, as well as to other cranial nerves. This impression receives support from the writings of Wolff[21] and Grigorowsky.[22] One would expect, and our dissections have shown, that the oculomotor nerve is supplied by vessels which lie in close proximity to it. They give rise to a series of nutrient arteries of small size, which approach the nerve at right angles and then divide into branches which course the entire length of the nerve trunk within the epineurium, anastomosing with branches of other nutrient arteries. These vessels which course in the epineurium customarily give off small branches which penetrate the perineurium and terminate in a longitudinally arranged network of arterioles and capillaries that lie between and within the nerve fasciculi. The inter- and intrafascicular vascular bed can be followed the full length of the nerve.

In order to determine the exact origin of the major nutrient vessels which supply the various portions of the oculomotor nerve, we injected red-colored Neoprene (a polymer of chloroprene) into the basilar and internal carotid arteries in four cadavers at the time of postmortem examination and dissected the nerves with the help of a dissecting microscope. By this method it was possible to demonstrate the blood supply of the trunk and the intraorbital part of the oculomotor nerve. We observed that two or three small arteries arise from the posterior cerebral or the superior cerebellar arteries and enter the nerve at right angles at a point where it crosses these vessels. These small arterial branches divide into two epineurial twigs, which course longitudinally. Similarly, at the peripheral end of the nerve it was possible to demonstrate within the orbit that the two terminal divisions of the oculomotor nerve are supplied by small recurrent arteries which arise from branches of the ophthalmic artery at a point where this vessel supplies the extraocular muscles in the posterior part of the orbit close to the annulus of Zinn. These vessels, which from case to case are variable in number and location, appear to arise from the lacrimal and superior external muscular branches of the ophthalmic artery, and to penetrate the epineurium of the nerve.

It was, on the other hand, most difficult to determine the vascular supply of the cavernous portion of the oculomotor nerve. Within the cavernous sinus, despite the close proximity of the third nerve to the internal carotid artery siphon, no vessel could be traced from its wall to the third, fourth, or sixth nerves. The arteries supplying the meninges, the Gasserian ganglion, and the pituitary gland were readily identified. However, we were not confident in the accuracy of our observations, since we could not inject the common or external carotid arteries in human material for reasons beyond our control, and dissection of these vessels is difficult. In order to obtain more information about this part of the nerve, we undertook to inject the common carotid arteries of several rabbits and cats and one dog. In rabbits and cats we observed that the cavernous portion of the third nerve is at times supplied by a separate small branch which originates on the main trunk of the external carotid or the middle meningeal artery. No branches were seen coming from the internal carotid artery. In some animals the branch supplying the oculomotor nerve also supplied the

ophthalmic division of the fifth nerve. We noted a great deal of variation between one side and the other in the same animal, as well as between animals. In the dog which we injected and dissected in a similar manner, it was noted that the third nerve within the cavernous sinus was supplied by a small branch which originated on an anastomotic channel between the external and internal carotid arteries.

Since the exact vascular pattern of the case under discussion is not known, one can only postulate that the nutrient artery supplying the anterior cavernous portion of the left oculomotor nerve (assuming the presence of such a vessel in this case) may have carried an important part of the blood supply to this nerve. If this vessel had become occluded by thrombosis at a site prior to entering the nerve, infarct necrosis could have occurred in the distal intracavernous portion of the third nerve.

Our case established that at least some instances of diabetic ophthalmoplegia are probably due to lesions in the orbital or retro-orbital parts of the affected nerve. We have failed to identify the nature or exact site of the lesion or to prove its specific relationship to diabetes mellitus. We cannot even be sure that it differs from the lesions which must account for some of the unexplained ophthalmoplegias of nondiabetic patients.

V. Summary

A case of oculomotor nerve palsy occurring in a 62-year-old diabetic woman who died five weeks following the onset of her illness as a result of carotid arteriography is reported.

The general pathological findings were edema and hemorrhage into the larynx, trachea, and upper esophagus; generalized atherosclerosis; intercapillary glomerulosclerosis (Kimmelstiel-Wilson disease); hyalinized islets of Langerhans; retinitis proliferans and aneurysmal dilatation of the retinal veins, and an oculomotor neuropathy.

The major pathological changes in the left oculomotor nerve were a fusiform enlargement of the retro-orbital part of the nerve; destruction of some of the myelin sheaths and axis cylinders in the center of the nerve; an increase in epi-, peri-, and endoneurial connective tissue and suggestive evidence of regeneration in the area of destruction; Wallerian degeneration in the distal segment; axonal reaction in the left third nerve nucleus in the midbrain, and arteriosclerosis of the vasa nervorum.

The lesion possessed features which were believed to be compatible with an incomplete ischemic neuropathy. However, serial sections of the nerve failed to demonstrate an occluded artery or vein. The possibility of occlusion of a nutrient artery outside the nerve is postulated as the most likely cause of the lesion. Examples from the literature are cited in support of this idea. The findings of a series of dissections of the vascular supply of the oculomotor nerve in humans and laboratory animals are summarized.

Dr. John Strom assisted in the detailed dissection of the ocular nerves and muscles during the autopsy, and Miss Margaret Carroll prepared the histopathological material.

Massachusetts General Hospital (Dr. Adams).

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Studies on the Diethylamide of Lysergic Acid (LSD-25)

II. Effects of Chlorpromazine, Azacyclonol, and Reserpine on the Intensity of the LSD-Reaction

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The effects of "tranquilizing" drugs on the abnormal mental state induced by the diethylamide of lysergic acid (LSD-25) are of interest from several points of view. Some means of mitigating too severe a reaction is needed in using LSD-25 experimentally or therapeutically. Since the LSD reaction is measurable and reproducible,[1] it might be possible to use the LSD psychosis as a screen for predicting the potential clinical value of new tranquilizing drugs. In addition, such studies might be useful in elucidating the mechanisms of action of both the tranquilizers and the psychotogenic drugs. The purpose of the present paper is to present the results of experiments in which attempts were made to block (prevent) or reverse (treat) the LSD reaction with chlorpromazine, azacyclonol (Frenquel), and reserpine.

Methods

Subjects.—The subjects used in these experiments were all adult male drug addicts who were serving sentences for violation of the Harrison Narcotic Act. All subjects volunteered for the experiment; none were psychotic, and the majority had been diagnosed as having character disorders or inadequate personalities. All had been abstinent from opiates for three months or more prior to serving in the experiments. The LSD reaction in such subjects has been shown to be similar to or identical with that in persons who have never been addicted to narcotics.[1]

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Means of Measurements and Analysis.—These have previously been described in detail.[1] The patellar reflex, pupillary size, and resting systolic blood pressure were measured hourly for two hours prior to and eight hours after administration of the LSD. The data were plotted on graph paper; the average of the two pre-LSD measurements was used as a base line and the area under the curve measured with a planimeter, thus converting all the data for that particular subject and that particular day to one figure. The mental effects were assessed by administering the questionnaire devised by Jarvik et al.,[2] hourly, two hours before and eight hours after administration of LSD. The number of positive responses after LSD were counted, eliminating any positive answers that were also scored positively prior to administration of the drug. The intensity of the reaction was graded on a 4-point scale, using criteria previously described. The grade was based on a short psychiatric examination which was carried out either at the height of the reaction or hourly.

Drugs.—LSD and an LSD placebo were given orally to fasting patients in doses specified below. Chlorpromazine and azacyclonol were administered either before (blocking experiment) or at the height of the reaction after LSD (reversal experiment). Only blocking experiments were conducted with reserpine. The specific doses of the tranquilizers, routes of administration, and times are described below under the specific experiments. Experiments were conducted at least one week apart in order to prevent the development of tolerance to LSD.

Experimental Design.—A "cross-over" design, in which each person served as his own control, was used. Study of any tranquilizer always involved four separate drug combinations in the same group of subjects: LSD placebo plus tranquilizer placebo; LSD plus tranquilizer; LSD placebo plus tranquilizer; LSD plus tranquilizer placebo. The "double-blind" pro-

TABLE 1.—*Effect of Chlorpromazine in "Blocking" the LSD Reaction*

NUMBER OF SUBJECTS	DOSE OF LSD MCG	DOSE OF CHLORPROMAZINE (1) MG	RESULT
6	40	50	MENTAL REACTION (CLINICAL GRADE) AND NUMBER OF QUESTIONS REDUCED SIGNIFIGANTLY
7	40	75	MENTAL REACTION, PATELLAR REFLEX, AND BLOOD PRESSURE REDUCED SIGNIFIGANTLY
19	60	75	MENTAL REACTION AND PUPILLARY REACTION REDUCED SIGNIFIGANTLY
7	60	100	MENTAL REACTION AND PUPILLARY REACTION REDUCED SIGNIFIGANTLY

(1) GIVEN AS A SINGLE DOSE ORALLY, 30 MINUTES PRIOR TO LSD

cedure was followed throughout. Both the observers and the subjects were unaware of the medication that had been administered. The order in which the various combinations of LSD and tranquilizers were given was randomized by using random numbers and a Latin-square design.

Results

Chlorpromazine.—Four blocking experiments were done with chlorpromazine, which was given orally 30 minutes prior to LSD. The timing was such that maximal effects of chlorpromazine and LSD developed simultaneously. The drug combinations used were 50 mg. of chlorpromazine HCl against 40γ of LSD-25; 75 mg. of chlorpromazine HCl against 40γ of LSD-25; 75 mg. of chlorpromazine HCl against 60γ of LSD-25, and 100 mg. of chlorpromazine HCl against 60γ of LSD-25. The data are summarized in Table 1. A significant reduc-

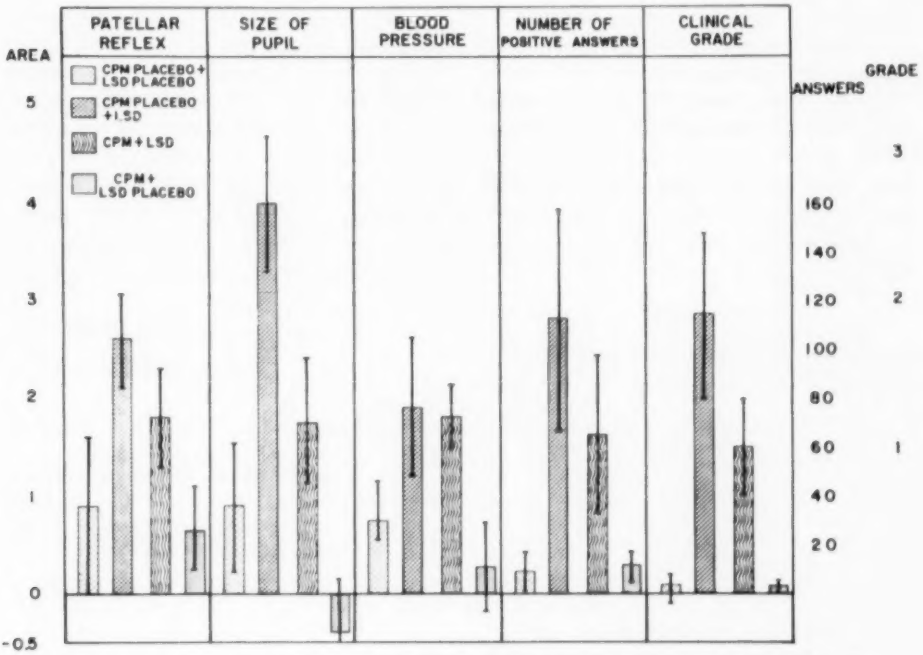

Fig. 1.—Effect of 75 mg. of chlorpromazine HCl given 30 minutes before LSD. For details see text.

tion in intensity of the mental effects produced by LSD was observed in all experiments. Detailed results of the largest experiment, in which 75 mg. of chlorpromazine HCl was given 30 minutes prior to 60γ of LSD-25 in 19 subjects, are shown in Figure 1. In this, and in subsequent figures, the means of the various measurements under the four treatment conditions are represented by the heights of the bars. The kinds of treatments are identified by differing hatching on the bars. The heavy lines with brackets at the top of the bars depict two standard errors above and below the mean of that particular measurement and treatment combination. In order to show a statistically significant difference between LSD alone and tranquilizer plus LSD, the bracketed lines of the two center bars should not overlap. In Figure 1, the size of the pupil and the clinical grade of reaction after LSD plus chlorpromazine are significantly reduced, as compared with LSD plus chlorpromazine placebo. Although the knee jerk, blood pressure, and number of positive answers were not diminished significantly, a trend to reduction in these measurements was present.

In the doses used, chlorpromazine did not abolish the mental effects of LSD completely. Anxiety, increased psychomotor activity, and nervousness were less prominent, and fewer patients reported visual perceptual distortion and hallucinations. Confusion and difficulty in concentration and thinking, however, persisted despite the chlorpromazine.

Two reversal experiments with chlorpromazine are summerized in Table 2. In the first experiment 75 mg. of chlorpromazine HCl was given orally one and one-half hours after 60γ of LSD-25. Although pupillary size was reduced by the chlorpromazine, the over-all course of the mental reaction was not significantly affected. Since chlorpromazine given orally requires about two hours to develop maximal effects, and since the LSD reaction is already beginning to subside by the time the chlorpromazine would have exerted its maximal effect in this experiment, the failure to show any change in the total course of the reaction is not surprising. Significant amelioration was attained in the second experiment, in which 25 gm. of chlorpromazine HCl was given intramuscularly one and one-half hours after a variable dose of LSD-25. Results with chlorpromazine intramuscularly are particularly significant, since the dose of chlorpromazine was not large and the dose of LSD was sufficient to induce a Grade 3 reaction in all subjects.

Azacyclonol.—One blocking (preventive) experiment was done with azacyclonol. Twelve patients received 20 mg. of azacyclonol HCl orally (or placebo) every eight hours for seven days and an additional 20 mg. of azacyclonol HCl two hours before administration of 60γ of LSD-25 on the day of the experiment. The tests were carried

TABLE 2.—*Effect of Chlorpromazine in "Blocking" the LSD Reaction*

NUMBER OF SUBJECTS	DOSE OF LSD (MCG)	DOSE OF CHLORPROMAZINE (MGM) AND ROUTE (1)	RESULT
12	60	75 "O" (2)	PUPILLARY SIZE REDUCED; MENTAL REACTION NOT AFFECTED
12	60-150	25 "I.M." (2)	MENTAL REACTION AND PUPILLARY SIZE REDUCED SIGNIFICANTLY

(1) GIVEN 1 1/2 HOURS AFTER LSD

(2) "O" REFERS TO ORAL ROUTE OF ADMINISTRATION; "I.M." TO THE INTRAMUSCULAR ROUTE

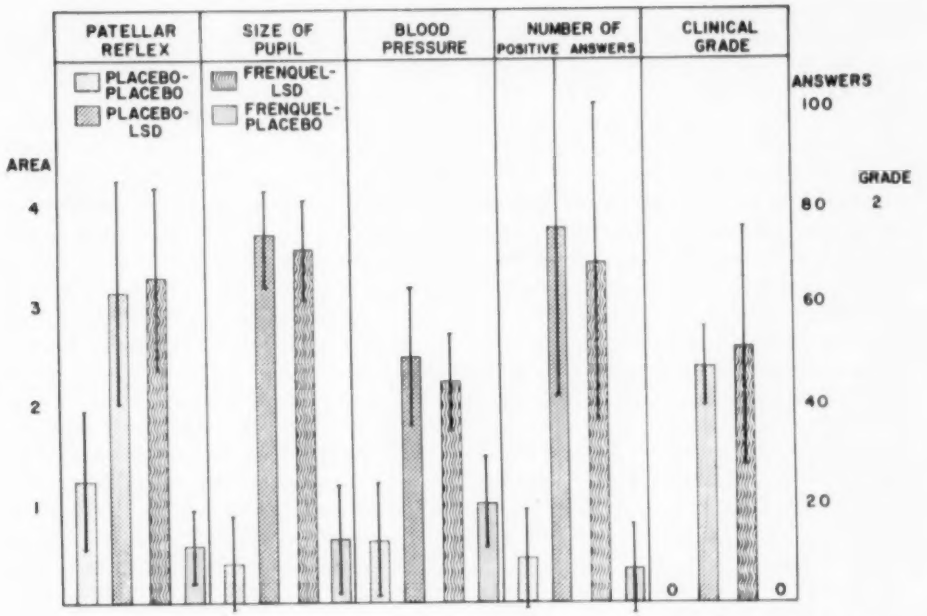

Fig. 2.—Lack of effect of azacyclonol (Frenquel) given before LSD. For details see text.

out at intervals of two weeks in order to permit "washout" of azacyclonol, which has been reported by Fabing [2] to have an effect persisting for a week. Results in this experiment are shown in Figure 2. No reduction in any aspect of the LSD reaction occurred. In this experiment, the mean degree of mental effect after LSD alone was not great, being only slightly above Grade 1. Two of the twelve patients, however, had hallu-

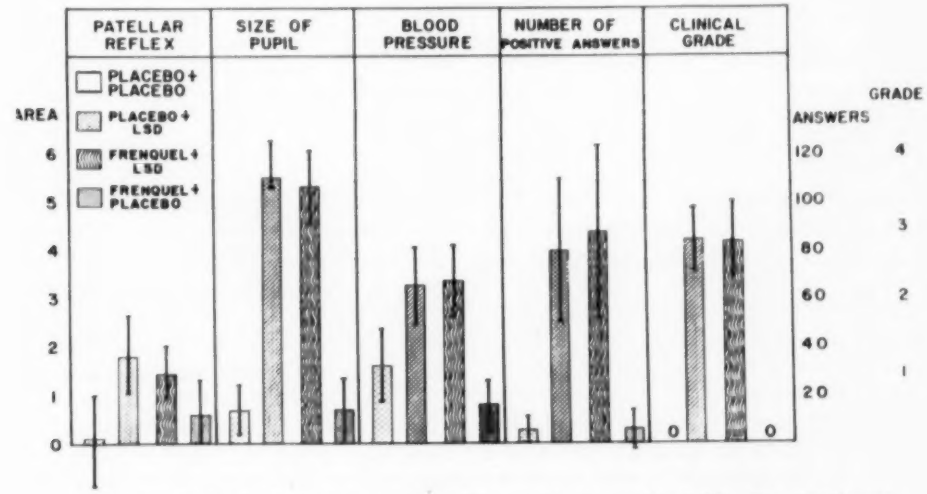

Fig. 3.—Back of effect of azacyclonol (Frenquel) given after LSD. For details see text.

cinations regardless of whether or not they had received azacyclonol.

In a reversal experiment, 12 patients received varying doses of LSD-25 (2γ-3γ /kg.) The dose was chosen individually in order to induce a Grade 3 (hallucination) reaction in all subjects. Sixty milligrams of azacyclonol HCl (or an azacyclonol placebo) was given intravenously two hours after LSD. An additional 40 mg. of azacyclonol HCl (or placebo) was given intravenously three hours after LSD. The results are shown in Figure 3. No significant diminution in any aspect of the LSD reaction could be demonstrated after azacyclonol. Detailed statistical analysis of the effect of azacyclonol on the time course of the reaction as reflected by the number of positive answers reported each hour or by determination of the clinical grade hourly showed no significant change.

Reserpine.—Because of the slow onset of action of reserpine, only blocking experiments were attempted with this drug. The combinations used were as follows: 1 mg. of reserpine orally two hours prior to administration of LSD; 2.5 mg. of reserpine orally, 10 and 2 hours prior to LSD-25; 2.5 mg. of reserpine orally, 22, 10, and 2 hours prior to 60γ/kg. of LSD-25; 2 mg. of reserpine intramuscularly, 22, 10, and 2 hours prior to 60γ/kg. of LSD-25; 2 mg. of reserpine intramuscularly, 22, 10, and 2 hours prior to 0.5γ/kg. of LSD-25. The results are summarized in Table 3. There was no evidence of any mitigation of the LSD reaction by reserpine in any of the experiments. In fact, the patients seemed to be worse after receiving the larger doses of reserpine plus LSD than after LSD alone. The details of the experiment in which 6 mg. of reserpine (total dose) in 22 hours against 0.5γ/kg. of LSD are shown in Figure 4. The increase in the number of positive answers and in the clinical grade may be noted. This experiment was particularly significant, since the dose of LSD was small, so that beneficial effect of reserpine should have been easily detected.

The combinations of reserpine and LSD were so disagreeable that the patients were persuaded to complete all the experiments only with the greatest difficulty. In addition to the usual symptoms experienced after LSD, the patients reported other symptoms, which seemed to be of two sorts: first, the usual side-effects of reserpine, such as nasal stuffiness, nausea, diarrhea, vomiting, lethargy, weakness, and dizziness on standing; second, severer mental effects. The latter included nervousness and confusion, which exceeded that experienced after LSD alone. A specific kind of hallucination was frequently reported after the combination of LSD and reserpine, which the patients termed "jets" or "jet propulsion." This

TABLE 3.—*Effect of Reserpine in "Blocking" the LSD Reaction*

NUMBER OF SUBJECTS	DOSE OF LSD MCG	TOTAL DOSE OF RESERPINE MG AND ROUTE	RESULT
12	60	(1) 2.0 "O" (4)	NO BLOCKING
12	60	(2) 5.0 "O"	NO BLOCKING
12	60	(3) 7.5 "O"	NO BLOCKING; PATIENTS WORSE
12	60	(3) 6.0 "I.M." (4)	NO BLOCKING; PATIENTS WORSE
12	0.5/KG	(3) 6.0 "I.M."	NO BLOCKING; PATIENTS WORSE

(1) GIVEN IN ONE DOSE 2 HOURS PRIOR TO LSD
(2) DIVIDED IN 2 DOSES 10 HOURS AND 2 HOURS PRIOR TO LSD
(3) DIVIDED INTO 3 DOSES 22, 10 AND 2 HOURS PRIOR TO LSD
(4) "O" REFERS TO ORAL ADMINISTRATION; "I.M." TO INTRAMUSCULAR

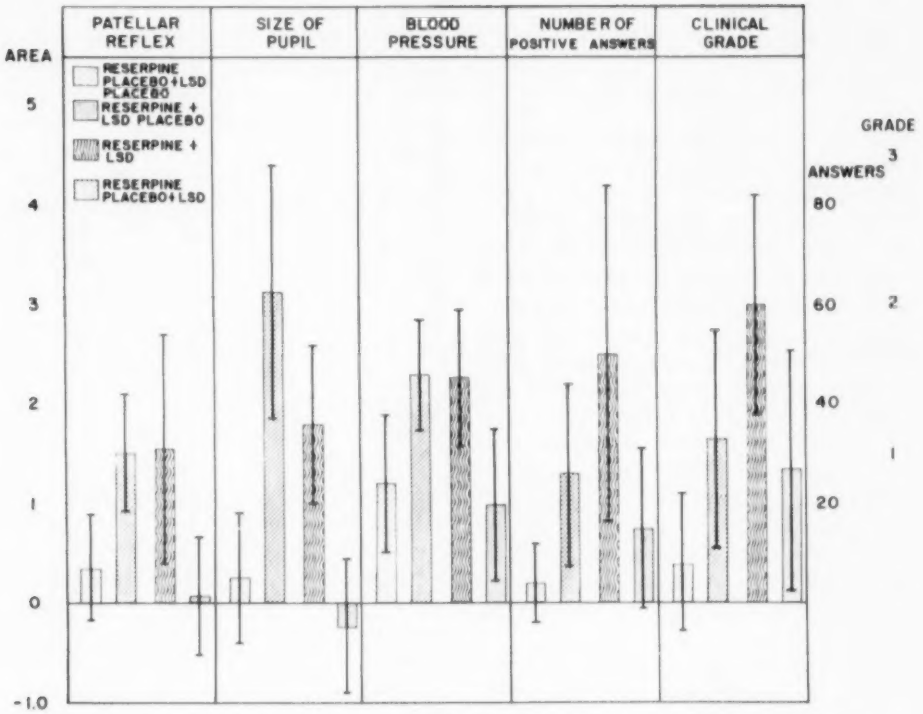

Fig. 4.—Effect of Intramuscular reserpine given before 0.5 mg/kg. of LSD. For details see text.

hallucination consisted of a repeated hissing sound which seemed to start in the back of the head and culminated in an expanding flash of light. Simultaneously, patients had a sensation of being hurled or of flying through the air. This particular hallucination was not observed under either LSD alone or reserpine alone.

The subjective effects of the large doses of reserpine in nonpsychotic patients are of some interest. While they were in no way as severe or as unpleasant as those after the combination of reserpine plus LSD, they were, under the circumstances of the experiments, very disagreeable to the subjects. In addition to the expected side-effects of reserpine, such as nausea, the patients were nervous and apprehensive, even though they were lethargic and weak. Mental confusion, depression of mood, and irritability were consistently reported. Most patients heard buzzing sounds, which did not culminate in the flash of light customarily reported with the combination of LSD and reserpine. Two of the twelve patients reported illusions of lights with the eyes closed. These lights were shimmering little dots of white light and differed from the kaleidoscopic play of colors seen when under the influence of LSD. To what extent the subjective effects of reserpine were colored by the fact that all the patients received LSD cannot be determined.

In addition to increased subjective complaints, neurological changes were enhanced after the combination of LSD and reserpine. These consisted of gross tremors at rest, involving large muscle groups in arms and legs in 7 of the 12 patients who received 60γ of LSD-25 plus 6.0 mg. of reserpine intramuscularly. While such tremors may occur after larger doses of LSD alone,

they were not present after 60γ of LSD-25 alone in these patients.

Comment

Of the three drugs tested, only chlorpromazine reduced the intensity of the LSD reaction significantly. This appeared to be due to the sedative effects of the chlorpromazine and was not due to a specific antagonistic action, such as is observed when nalorphine (*N*-allylnormorphine) is administered after morphine. The results with chlorpromazine are in agreement with those reported by Hoch[3]; Schwarz, Bickford, and Rome,[4] and Giberti and Gregoretti.[5]

Failure of azacyclonol to alleviate the LSD reaction is puzzling in view of the enthusiastic reports of Fabing.[2,6] We have no explanation for the differences in our results and those of Fabing except differences attributable to the type of subjects, the experimental environment, and the experimental design.

Failure of reserpine to mitigate the LSD reaction is in agreement with the results of Hoch,[3] but in disagreement with those of Giberti and Gregoretti.[5] The differences between the results reported here and those of these authors are possibly due to differences in the dosage of reserpine and methods of measurement and experimental design.

A number of hypotheses are currently being advanced which relate serotonin to mental functioning and the LSD psychosis to some interference with, or enhancement of, serotonin effects within the central nervous system. Woolley and Shaw[7] postulated, on the basis of similarity in chemical structure of LSD and serotonin, and of antagonistic effects of the two drugs on isolated smooth muscle preparations,[8,9] that LSD might cause a psychosis by interfering with serotonin within the central nervous system. In this first paper[7] Woolley and Shaw mention only the possibility of deficiency of serotonin produced by competition of serotonin with LSD for receptor sites in neurons, but in a latter paper[10] they state that an alternative hypothesis is possible which relates the LSD psychosis to an excess of serotonin caused by inhibition of amine oxidase by serotonin antagonists. Shore, Silver, and Brodie[11] have shown that both reserpine and serotonin prolonged sleeping time after hexobarbital in mice and that LSD abolished the prolongation. These authors[12] suggest that serotonin has an important function in the brain and that LSD produces its mental disturbances by suppression of some central action of serotonin. In other experiments the same group of investigators have demonstrated that reserpine reduces the concentration of serotonin in the brain,[13] as well as in the intestine[14] and blood platelets. The hypothesis advanced by these workers has, however, been greatly weakened by demonstrations that 2-brom-*d*-lysergic acid diethylamide (BOL), a substance which does not induce a psychosis in man, both blocks the smooth muscle spasm induced by serotonin[15] and abolishes serotonin or reserpine-induced enhancement of sleeping time in mice and rats.[16] Obviously, these phenomena can have no relationship to the psychomimetic effect of LSD in man.

Costa[17] found that in low concentrations, such as would be found in clinical experimentation, LSD enhanced the spasmogenic action of LSD on the excised rat uterus, while higher concentrations blocked this effect. Mescaline always augmented serotonin-induced uterine contractions, whereas azacyclonol, reserpine, and chlorpromazine inhibited the uterine spasm caused by serotonin. On this basis, Rinaldi, Rudy, and Himwich[18] suggested that the psychotogenic effects of LSD and mescaline were due to their serotonin-facilitating properties and that the correction of LSD-evoked psychosis by azacyclonol was due to inhibition of serotonin.

If, as seems probable, reserpine caused a release of serotonin from nerve tissue in our patients, this additional serotonin had no ameliorating effect on the LSD reaction. Since our patients were worse after reserpine, our results favor the hy-

pothesis which relates the LSD psychosis to an excess of serotonin rather than the hypothesis which postulates a deficiency of serotonin. Such an interpretation, however, should be viewed with caution, since reserpine alone did not produce a psychosis identical with that caused by LSD, as would be expected if excess of serotonin-like action were the only mechanism of the LSD effect. In addition, it was not possible in our experiments to determine whether the increased objective and subjective effects seen after the combination of LSD and reserpine were due to a specific enhancement of the LSD effect by reserpine, or were due merely to a combination of two kinds of drug toxicity.

Winter and Flataker[19] have found that both LSD and reserpine impair the ability of hungry rats to climb a rope in order to obtain food. Serotonin blocked this effect of LSD, whereas reserpine enhanced the impairment of performance after LSD. Winter's results with the combination of reserpine and LSD are in the same direction (enhancement of the LSD effect by reserpine) as those reported here. Since, however, serotonin ameliorated the LSD reaction in rats, the serotonin presumably "released" by the reserpine must have been prevented from blocking the LSD response because of some other action of reserpine. At the moment there is no single hypothesis which explains satisfactorily all the data on the interrelationships of LSD, serotonin, and reserpine.

Correlation of results in our experiments and those obtained in experiments utilizing isolated smooth muscle or neurophysiological techniques in animals are very poor. For example, Costa[17] found that azacyclonol, reserpine, and chlorpromazine all antagonized serotonin-evoked contraction in the isolated rat uterus. Since in our experiments only chlorpromazine reduced the intensity of the LSD psychosis, these results seem to have little bearing on the mechanism of the LSD effect in man. Rinaldi and Himwich[20] found that azacyclonol reversed the LSD- and mescaline-induced electroencephalographic changes in the rabbit; yet it is clear that azacyclonol had no ameliorative effect on the LSD psychosis in man. Purpura[21] found that reserpine antagonized both LSD-induced facilitation and depression of electrical responses in the cortex of the cat which were evoked by auditory stimuli. Since reserpine does not block the psychotogenic effect of LSD in man, the significance of this observation is obscure.

The results with reserpine make it unlikely that the LSD psychosis can be used as an effective screen for drugs that might be useful in the pharmacotherapy of mental illness.

Summary

1. Chlorpromazine ameliorates partially the abnormal mental state induced by the diethylamide of lysergic acid (LSD-25) in man. Chlorpromazine has this effect when administered before or after LSD.

2. Azacyclonol (Frenquel) does not reduce the intensity of the LSD psychosis in man.

3. Reserpine does not mitigate the LSD psychosis in man. Patients receiving a combination of reserpine and LSD have severer symptoms than when receiving either drug alone.

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Studies on Phenylketonuria

VI. EEG Studies in Phenylketonuria

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Phenylketonuria is a condition in which there is an inherited biochemical defect in the normal oxidation of phenylalanine to tyrosine. This abnormality was first recognized and described by Fölling[1] in 1934; the term phenylketonuria, suggested by Penrose and Quastel,[2] has been used by many recent investigators. Extensive clinical reports[3-8] and further chemical investigations of urine,[9-13] blood,[4,5,7,11-18] spinal fluid,[14] and brain[19,20] have been published subsequently.

Persons with this defect are almost always mentally retarded, usually to a severe degree. Most authors make no comment, or only incidental mention, of seizures in patients with phenylketonuria, but Cowie,[16] Woolf and Vulliamy,[4] and Bosma and associates[8] have commented upon the frequency of coincident epilepsy. Penrose[21] mentioned in 1946 that some affected children had seizures but that he had never observed them in phenylketonuric adults. The incidence of this disease in the population at large is not known; the frequency in institutions for retarded children was found to be 1% in the northeastern United States by Jervis,[13] 1% in Utah, 1.2% in Britain,[22] and 0.04% in Switzerland.[23]

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Because this metabolic entity has been well studied chemically and clinically, because we find seizures frequently,[4,8] and because control of the chemical aberrations has been achieved by dietary means, phenylketonuria lends itself well as a model for electroencephalographic (EEG) studies of metabolic disease affecting the brain. Previous EEG recordings on phenylketonuric patients have been reported by Gibbs and Gibbs;[24] by Woolf and Vulliamy[4] in the waking state, and by Fois and collaborators during sleep,[25] and a summary of results with several patients has been reported by Cowie.[16]

Clientele and Methods

Our material is based on 94 EEG's of 23 phenylketonuric patients. Eleven patients are inmates of the Utah State Training School in American Fork; one is an outpatient brother of an inmate; eleven children were seen and examined in the offices of the department of pediatrics, University of Utah College of Medicine. The patients' ages at the time of the first EEG examinations ranged from 7 months to 47 years, 10 children being less than 4 years of age and the only 2 adults being over 40. The mental development varied from a completely helpless existence to an I.Q. of 82 in a 2½-year-old girl.[26] Among the 23 subjects, there were 3 children from one sibship and three instances of 2 children from the same family; 10 were male and 13 female.

On 10 patients we could obtain a report of seizures. It is of interest to note that among the 12 patients seen at the Training School we elicited a history of grand mal in only 3 and of other kinds of seizures in only 1, namely, the brother of 2 outpatients. In the 11 cases from the pediatrics department of the College of Medicine, the investigators took the history directly from the parents themselves, and in these cases a positive seizure history was obtained in 6. These six children and the above-

mentioned inpatient had the type of seizure that is called infantile spasm,[27,28] or massive spasm.[29] Two of these children also had grand mal convulsions.

The EEG's were obtained with a Grass Model III, eight-channel electroencephalograph with unipolar recordings in all records and bipolar technique in many. Sleep was used as activator of seizure discharges in all but one patient.[30]

Results

Six patients had typical hypsarhythmia[27,28] during sleep; the five youngest patients of the group were among these. The sixth child who had hypsarhythmia did not have this severest form of dysrhythmia at the ages of 1 and 3 years but first was shown to have this disorder when he was 7 years old. His I.Q. is below 10; he cannot walk, has no speech, and cannot feed himself. In three of these six children the hypsarhythmia was not apparent until the patients had fallen asleep.

Multiple spike seizure foci were found on at least one recording of three children; all three were less than 2 years old at the time of examination.

Occipital and temporal spikes were seen in children within an age range from 8 months to 13 years, with no difference in age distribution between the two types of foci. Spikes from the frontal and parietal leads alone, or in addition to other foci, were seen in nine children between the ages of 2 and 9 years. Larval grand mal characterized by runs of generalized multiple spikes were seen in one recording each in a 12-year-old girl and a 46-year-old woman. The same woman also had 14- and 6-per second positive spikes in light sleep. The third oldest patient, at ages 18 and 20 years, had no seizure discharges, but his basic frequencies were slower than normal and he had additional paroxysmal slowing.

There was only one patient whose EEG's were classified as normal, according to Gibbs' standard,[31] on repeated examinations. He was the oldest patient in this series and had a waking record at age 47 and a sleep

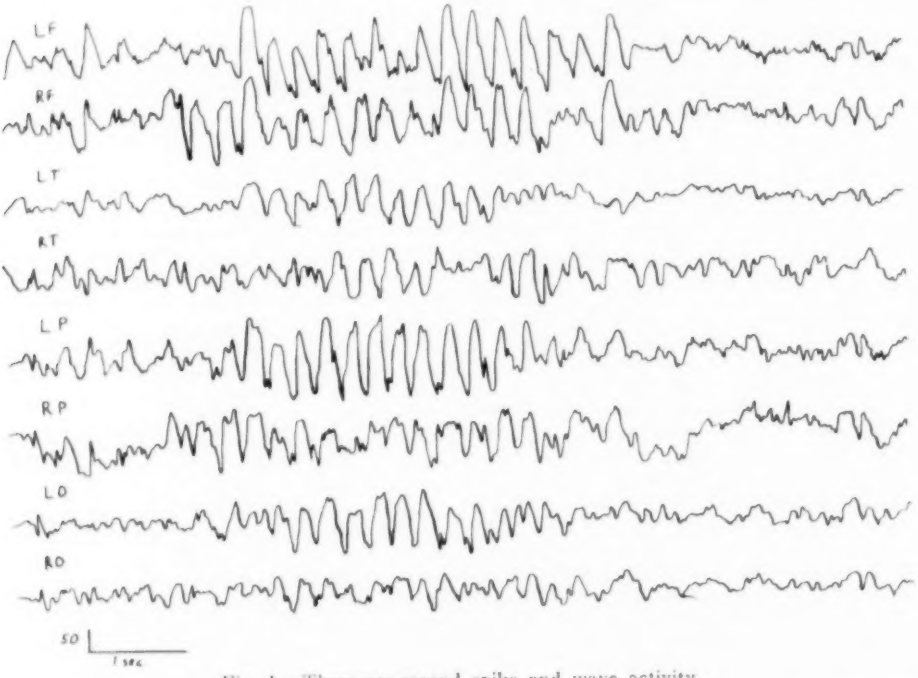

Fig. 1.—Three-per-second spike and wave activity.

record at age 49. His mental retardation is only moderate (I.Q. 67-74), and his blood phenylalanine level and excretion of abnormal metabolites are much lower than those observed in the other institutionalized patients (details cited elsewhere [26]). One patient with normal EEG's at 1 and 4 years of age had frontal and occipital spikes awake and asleep at age 6. She is quite severely retarded and overactive and has a blood phenylalanine of 84 mg. per 100 cc.

Of the 23 patients 7 had many spike-and-wave discharges of frequencies varying from 3 to 6 per second (Fig. 1). Although the rate varied somewhat among these patients, it was constant for each child. In three of these children these spike-and-wave discharges were highly similar to the findings in petit mal epilepsy. Their appearance was identical to the pattern illustrated by Fois, Rosenberg, and Gibbs [25] in phenylpyruvic patients. Woolf and Vulliamy [3] state that their Cases 1 and 5, between the ages of 1 and 2 years, had spike-and-wave complexes "typical of petit mal" in conjunction with clinical "petit mal." These seizures may well be the same kind of seizures that we call "infantile spasms." Their EEG complexes are probably the same as those described by Fois and associates and by ourselves.

TABLE 1.—*Principal EEG Findings in Patients Who Have Not Been on a Phenylalanine-Restricted Diet* *

Patient No.	Age	Principal EEG Finding
1	2 yr.	6 yr.
	Normal	F & O spikes
2	2½ yr.	
	T spikes	
3	2½ yr.	
	P spikes	
4	4 yr.	5 yr.
	F & O spikes	O & P spikes; hypsarhythmia
5	6 yr.	8 yr.
	Spike & wave	Spike & wave
6	6½ yr.	
	P spikes	
7	8 yr.	10 yr.
	T spikes	T & general spikes
8	8½ yr.	10½ yr.
	O Spikes	Spike & wave
9	9 yr.	
	T, P, & O spikes	
10	9½ yr.	12½ yr.
	F spikes	Slow; no spikes
11	10½ yr.	12½ yr.
	T spikes; spike & wave	Multiple general spikes
12	13½ yr.	
	T & O spikes	
13	18 yr.	20 yr.
	Slow; no spikes	Slow; no spikes
14	45 yr.	46½ yr.
	Normal waking	Larval grand mal, 14 & 6
15	47 yr.	49 yr.
	Normal waking	Normal sleep

* F indicates frontal; T, temporal; P, parietal; O, occipital.

TABLE 2.—*Principal EEG Findings Before Diet* Was Started*

Patient	Age	Principal EEG Finding
A.	9 mo.;	multiple foci awake, hypsarhythmia asleep
B.	7 mo.;	hypsarhythmia
C.†	3 yr.;	P & O spikes asleep
D.	4 yr.;	spike & wave; O Spikes
E.	23 mo.;	multiple foci
F.	15 mo.;	hypsarhythmia
G.	2 yr.;	hypsarhythmia
H.	23 mo.;	F & P spikes

* F indicates frontal; P, parietal; O, occipital.
† Patient C. was examined after diet was discontinued.

Because clinical control or improvement has been noted by several investigators [5,8,32,33] when children with phenylketonuria are maintained on a phenylalanine-restricted diet, electroencephalography has been used in the study of eight children on such a regimen (Tables 1 and 2). The patients reported by Armstrong and Tyler [7] are included in the present study.

A. (Case 4 [7]) was first seen before she was 10 months old; she had had many infantile spasms daily, and the parents gave a history of one convulsion. She had multiple spike foci while awake and severe hypsarhythmia in sleep on the EEG's recorded before the dietary treatment was commenced. Her blood phenylalanine level decreased to normal within two weeks, and her EEG improved. After she had been on a restricted diet for five months, she was given liberal amounts of phenylalanine for two months and then returned to the restricted diet a second time. Her clinical picture improved slowly on the restricted diet, worsened slowly when phenylalanine was returned to her diet, and improved rapidly when phenylalanine was again removed from her diet. Her EEG changes were roughly parallel to the clinical worsening and improvement, but were less prompt and less marked than the clinical response.

B. (Case 5 [7]) showed a severe hypsarhythmia and was started on the dietary regimen at 8 months of age (Fig. 2). He was examined frequently and followed closely during 20 months on the diet. His infantile spasms diminished in number markedly within less than one week of the initiation of diet. These seizures improved, and grand mal appeared clinically for the first time. A similar result in one child has been reported by Woolf and associates.[6] On the EEG, the hypsarhythmia was replaced by a few occipital and temporal

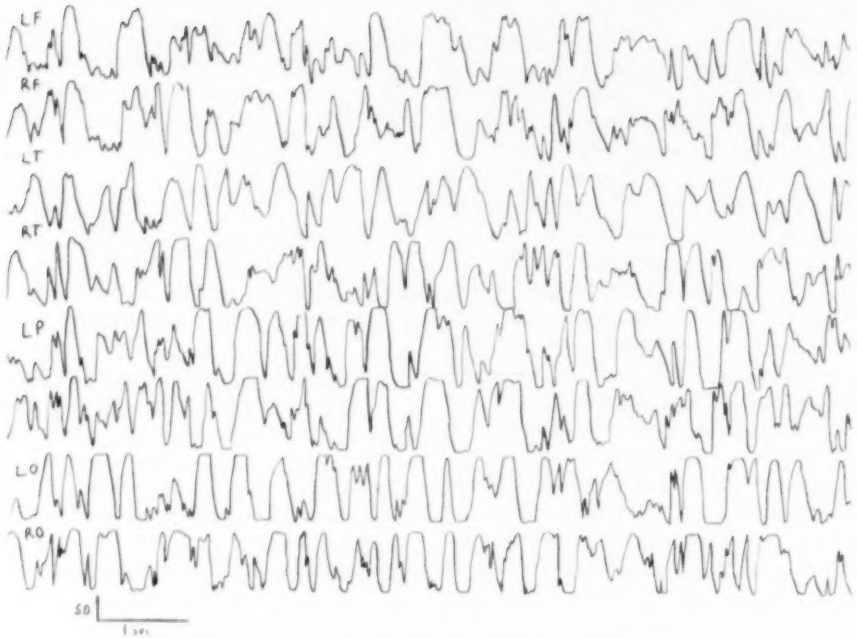

Fig. 2.—Patient B. before treatment; hypsarhythmia.

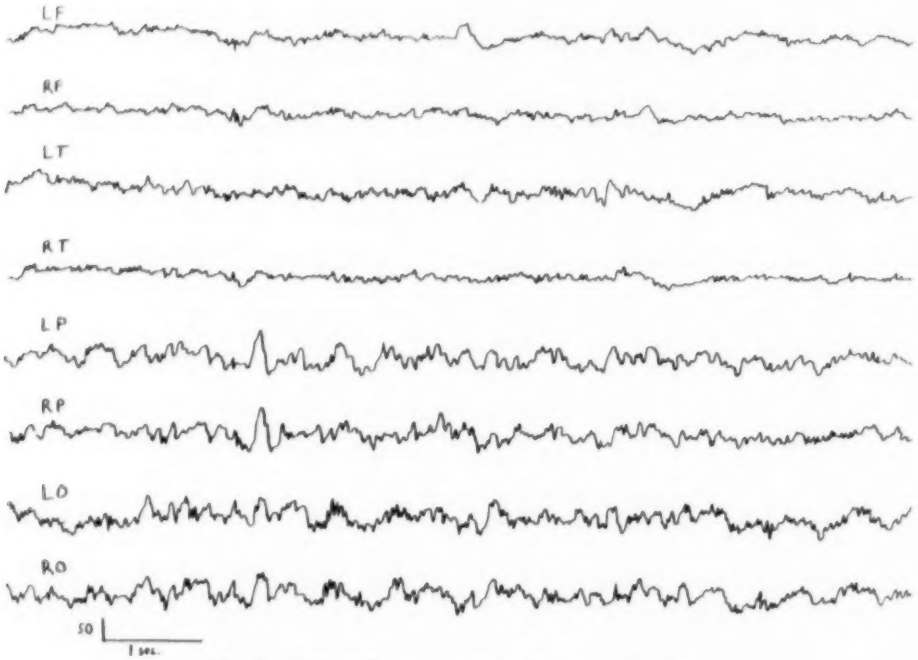

Fig. 3.—Patient B. on restricted diet; normal EEG.

spikes. Thirty-four days after the diet was started, and at a time when his blood phenylalanine level had been normal for two weeks, his last convulsion occurred (Fig. 3). He has been free of seizures in any form since June, 1954. All his waking EEG's have been normal subsequently, and sleep recordings have shown only a few spike seizure discharges. The phenylalanine-restricted diet was discontinued in January, 1956 (age, 27 months). Two months after the diet was discontinued, 3½ to 4 cps spike-and-wave discharges appeared for the first time, and many occipital spikes were present in June, 1956.

B.'s sister, C. (Case 3[7]), had her only EEG done one year after she had been on the diet for 10 months. She had a normal recording when awake and only a few parietal and occipital spikes in light sleep.

D. (Case 2[7]), a brother of C and B, was first examined when he was 48 months old. He had a history of infantile spasms, and his EEG showed almost continuous seizure activity, consisting of 3-6 cps spike-and-wave discharges and very many occipital spikes. He was on a phenylalanine-restricted diet for three months following his initial EEG. Two recordings obtained while he was on the diet and one 11 days after the diet was discontinued were normal. Seizure patterns were present again 20 days after he was given liberal amounts of full protein.

E. has no history of any kind of seizures. Before dietary treatment was instituted, she had multiple spike seizure foci on the waking EEG, worse during sleep. On repeated EEG's since that time, no seizure discharges have been found; dietary treatment is being continued.

F. was referred with the presenting complaint of seizures. They were typical infantile spasms according to the mother's description and our personal observation. Her EEG revealed continuous hypsarhythmia, without any periods of normalcy during waking and sleep. Her serum phenylalanine level was 61 mg. per 100 cc. at that time. Twenty days after the diet was instituted, when the phenylalanine level was normal, there was a very marked reduction in number and severity of seizures and the EEG revealed generalized spike discharges with long periods of normalcy, even in sleep. We plan to continue her on the diet and follow her further course.

G. was started on the diet when he was over 2 years of age; he had had many infantile spasms and other minor motor seizures. Although his seizures were diminished and his attention span improved on treatment, there has been no appreciable change in his hypsarhythmia, which is marked in the waking and sleeping states. There has, however, been some question as to the adequacy of the dietary control with this patient.

H. received a phenylalanine-restricted diet between her third and fourth birthdays, without a significant change in abnormality between the pretreatment EEG and recordings taken while she was on the diet.

Comment

The results reported in this paper confirm the findings of Fois and associates[25] that nearly all patients with phenylketonuria show electroencephalographic abnormalities. The present series is of particular interest in that a considerable number of recordings were made on patients of a much younger age than had previously been studied. It may be significant that the younger patients, in general, demonstrated severer abnormalities than were seen in the older patients. This was true whether clinical seizures had been grossly apparent or not. It might be speculated that this may provide evidence that an active process of cerebral damage could be occurring at an early age, and that the active process no longer continues in older patients, but that they continue at a level of mental functioning established by the extent of damage that occurred when they were very young.

Electroencephalography has been of importance in the efforts to evaluate, as objectively as possible, changes or improvements in the status of phenylketonuric patients who have been maintained on phenylalanine-restricted diets. In most cases in which there have been conspicuous EEG abnormalities, with or without apparent clinical seizures, the EEG's have been improved and in some cases normalized; in three of the five cases with clinical seizures the seizures ceased to occur, and in the fourth they were considerably improved in less than three weeks. Further evidence of actual improvement lies in the observation that in three cases studied in which there was an improved EEG the restoral of phenylalanine to the diet resulted in a de-

layed appearance of the abnormal EEG's. These findings support the idea that at least some of the pathological symptoms in phenylketonuria occur as the result of the presence of some toxic substance that is no tients given phenylalanine-restricted diets longer present when their blood level of many of the signs of improvement in paphenylalanine is lowered to normal. Indeed, may occur as the result of the observed lessening in EEG abnormalities.

Summary

Young phenylketonuric children frequently have seizures, usually in the form of infantile spasms. In that age group, hypsarhythmia and multiple seizure foci are found on electroencephalography. As these children grow older, they may have tonic-clonic convulsions, and their EEG's tend to show focal or generalized spike discharges. Of 23 patients, 7 had spike-and-wave complexes that were similar to those found in petit mal epilepsy. Only one adult had normal EEG's.

EEG patterns vary with age,[31,34-36] regardless of etiology.

Eight patients undergoing treatment with phenylalanine-restricted diet had EEG examinations. Five of these showed an EEG improvement on the diet; two in this group showed increasingly abnormal EEG's when treatment was interrupted. In two other children no remarkable EEG changes could be noted. The eighth patient had only one EEG recorded.

These studies suggest that the phenylalanine-restricted diet has beneficial effect on seizures and EEG's of phenylketonuric children. A warning of caution against overinterpretation should be sounded, however, because EEG's will change with age, with stage of waking, drowsiness, and sleep, and only EEG's obtained under very similar conditions should be compared.

Dr. Madison Thomas, director of the EEG Laboratory of the Salt Lake County General Hospital, and the EEG technicians collaborated in obtaining the recordings.

Dr. Frank Tyler, Department of Medicine, University of Utah College of Medicine, provided care in the metabolic ward for three of the children studied.

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The Illusory Awareness of Body Parts in Cerebral Disease

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For many years, neurologists have noted various complicated mental phenomena involving the body image in certain patients with organic disease of the brain. The clinical pictures have been characterized by distortion and defects in the awareness of his body parts, or, less often, of those of persons about him. The underlying pathological processes have been of degenerative nature or due to vascular or neoplastic disease.

Most recently, the subject has been excellently summarized by Critchley, of England, in his monograph "The Parietal Lobes."[1] In this country, Weinstein and Kahn[2] have made a number of valuable studies on the same matter. Before proceeding to our presentation of five unusual cases, we should like to present the views of these investigators. Critchley regards such alterations in the body image (or body schema) as due often, though not invariably, to disease of the parietal lobe, usually on the nondominant, i.e., right, side. He offers the following classification, which is admittedly imperfect and indistinct in its lines of cleavage. In a given case the symptoms fluctuate and the clinical picture may change from one group to another. In many cases it would appear that a fundamental psychic basis for these abnormalities lies in a denial of illness, epecially of a left hemiplegia.

In the accompanying Table (after Critchley), the symptom complexes are enumerated, beginning with the mildest form and progressing to the most marked, but even in this series the intensity of the symptomatic display is not reflected in this progression.

Classification of Disturbances of Body-Image Awareness Due to Central Nervous Disease *

1. Unilateral neglect
   - Motor; sensory; visual
   - Tactile inattention
   - Allochiria
   - Allesthesia (tactile, visual, auditory)
2. Lack of concern over existence of hemiparesis (anosodiaphoria of Babinski)
3. Unawareness of hemiparesis (anosognosia of Babinski)
4. Defective appreciation of existence of hemiparesis with rationalization
5. Denial of hemiparesis (or other physical defect)
6. Denial of hemiparesis (or other physical defect) with confabulation
7. Loss of awareness of one-half of body (with or without paralysis)
   - (Synonyms; asomatognosia, or hemiasomatognosia; imperception for one-half of body, or hemidepersonalization; autosomatamnesia or autosomatagnosia)
   - Segmental depersonalization (including denial of excreta, etc.)
   - Total asomatognosia (aschematia)
8. Hyperschematic (and paraschematic) syndromes
   - (a) Feeling of heaviness or swelling, deadness or lifelessness of parts
   - (b) Bipartition fantasy
   - (c) Illusions of corporeal transformation or of corporeal displacement
9. Phantom phenomena (viz., third hand), and phantom postures and movement with hemiplegia: as parts of focal epileptiform seizure: with paranoid projection mechanisms.

* After MacDonald Critchley: The Parietal Lobes, published by Edward Arnold & Co., London, 1953.

Study of our cases makes it evident that these categories overlap and shift, and that the condition may exhibit itself in very fragmentary form.

In a discussion of the possible sites of the lesion responsible for the eventual production of the above syndromes, Critchley makes the following comments: (1) that anosognosia is the consequence of diffuse lesions of the brain; (2) that it is the expression of disease of the subordinate parietal lobe, without specifying any particular region; (3) that it results from disease of the thalamus of the subordinate

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hemisphere (Schuster); (4) that it is due to lesions of the thalamoparietal peduncle within the subordinate hemisphere (Barkman, Hagen and Ives) (Nielsen would specify a lesion of the thalamosupramarginal fibers); (5) that it is the result of coincidental lesions of the parietal lobe and of the thalamus of the subordinate half of the brain (Poetzl); (6) that it is the consequence of a lesion of the callosal fibers (Hauptman).

While agreeing that anosognosia occurs with cerebral lesions at various levels, Critchley emphasizes that "the parietal lobe of the non-dominant hemisphere is the locus which most frequently comes under suspicion." He also emphasizes the abruptness of onset of the cerebral lesion, the variable involvement of the patient's sensorium, and the presence of motor weakness or sensory defect.

In a recent study of four cases, Weinstein, Kahn, Malitz, and Rozanski[3] described four instances in which there were delusional reduplications of parts of the body.

One patient with a left hemiplegia confabulated having an extra left hand; another with a left hemiparesis and a fracture of the right leg stated that he had four legs; a man with a cerebellar astrocytoma and meningitis confabulated having multiple heads, and a patient with a severe head injury who had previously had an eye enucleated expressed the delusion that he had several eyes. In all cases the symptom was of rapid onset and associated with a diffusely slow-wave EEG record.

In each case, reduplication of body parts was associated with other forms of reduplication of time, place and person. Accordingly, the phenomenon is considered but one manifestation of a general pattern of reduplicative delusions.

In their cases, disorientation, confusion, and impaired insight were obvious. There were "peculiar paraphasic naming errors[11] in three of their four cases, "the patient misnaming an object in terms of a single aspect of its structure or function." Alterations of sensory perception were apparent on double simultaneous stimulation, together with extinction and allesthesia. They refer to illusional postures of the limbs and movements, as well as the delusion of "extra" parts.

Weinstein and his co-workers "cannot ascribe the reduplication of a part of the body to the effects of the lesion that causes the incapacity of the part as in hemiplegia. It cannot be stated that the lesion produces reduplication by destroying that part of the brain, where 'awareness' of the existence, shape, form, or state of health of the limb is 'represented'." They believe that the peculiar symptoms arise as part of a reorganization of brain function, in which any member that the patient conceives of as damaged may be reduplicated no matter what the cause of the incapacity. Weinstein and his co-workers cite the case of Guthrie and Grossman.[4] The latter investigators tied down the right upper limb of a patient with a denial of hemiplegia on the left side. She then denied her inability to move the artifically immobilized right hand. This observation emphasizes the fact that the symptomatology can be shifted, and it might argue against a fixed locus of pathology.

Weinstein and associates point out that the "extra" part(s) are apt to be invested with symbolic qualities that arise in connection with certain conative drives and that these abnormal phenomena are symbolic expressions of the desire to be well. The lesion(s) produce a disturbance of brain function in which the patient denies whatever he feels is a threat, by way of a compensatory symbolic detour into an illusory pattern. So regarded, the authors do not believe we are dealing with a disturbance in body schema primarily; rather, the organic disease has set in motion a projection mechanism powered by conative forces in the interests of denial of illness and the bolstering of a faltering ego.

We would stress this interesting combination of circumstances as a striking example of organic brain disease activating so-called "functional" mechanisms.

In this connection, the above-named authors and others have pointed out that some of these patients have had abnormal

personalities prior to the onset of the organic brain disease. Weinstein and Kahn stressed feelings of insecurity with strong trends toward the expression of perfection and superiority; some patients reacted with feelings of guilt and associated anxiety; still others, with euphoria, compulsions, overmeticulousness, and worry.

Report of Cases

Case 1.—An electrical engineer, 58 years of age, had had hypertension (180/110) for many years. He was a very intelligent man, holding a position of importance.

On July 1, 1950, at about 7 p.m., he noticed blurred and double vision. The next morning, on awakening, he felt dizzy, found his right arm was "asleep," and veered to the right on walking.

On July 4 he was admitted to the Brooklyn Hospital, for the next six days, where various blood tests, including serology determinations, were found to be normal. The spinal fluid was not examined. There were loss of conjugate gaze to the left; right lateral nystagmus, greater in the abducted right eye; marked weakness of the left lower part of the face, and mild right-sided pyramidal signs. Considerable improvement set in. It was believed that a vascular thrombotic lesion had developed in the basilar arterial supply to the lower pons.

Toward the end of July, 1950, he complained of a feeling of soreness in the left side of his face and of puffiness about the left side of his mouth, and his walking was unsteady, due to ataxia. Nystagmus was present on looking to the right; paralysis of the left external rectus muscle was quite evident, and so was left facial paralysis of the peripheral type. There was bilateral extensor toe sign. On Aug. 28, he complained of numbness in his right hand; the dizziness had abated considerably, and the left side of the face was not as numb. The deep reflexes were increased on the right, and there was a right Babinski toe sign. Some outward movement of the left eye was noted. The blood pressure continued to register 180/110. On Sept. 14, there developed another attack, consisting of nausea, vomiting, staggering, and marked weakness of the left side, together with extreme loss of proprioception, as well as loss of pain, on the left side. The left extremities showed marked ataxia. There were right peripheral facial paralysis and a bilateral Babinski toe sign. On or about Sept. 25, his left arm began to feel very cold, and his wife noted that he seemed to regard the left upper limb in a peculiar, furtive manner. Under questioning by Dr. Merwarth, he admitted that he thought it belonged to someone else, more especially his daughter. At times he would pick up the left arm with the right to make sure that it belonged to him. These symptoms of false attribution of the limb soon were replaced by the feeling that a second (false) left hand and forearm had appeared at about the middle of the left forearm. For a time he was reluctant to tell his wife about these strange feelings, lest he be regarded as insane and be committed. The "parasitic" limb was foreshortened and was smaller than his real hand. He said: "The thumb and fingers are in the same position as my real hand. The new hand is cold and smaller. When I move my left hand, I feel as if the fake hand starts the movement and the real hand follows. I have no pain in it. The imaginary hand comes and goes. It is there in the afternoon, when my real left hand and forearm feel cold. It is so real that I rub my left arm with my right just to make sure that there is not an extra hand there. This fake hand is there at night, too, and it is also cold. I bundle up the left half of my body and arm to keep it and my real hand warm." By Oct. 7, the feeling that the left hand belonged to some other person had disappeared, but the imaginary left hand still persisted. Another complaint was unusual dreams and a strange feeling of being in an unusual place. About the same time vision in the left eye was impaired. "I can see well in the middle and make out the edges" (central scotoma). On examination he was unable to tell whether the left limbs were being moved, at any joint. There were a bilateral extensor toe response and right peripheral facial paralysis; the eyes were immobile. Hemorrhages were noted in the left retina. In mid-October, 1950, the left phantom hand was still present, perhaps a bit more distal in position, and he still had the feeling that the left phantom fingers initiated the movement of the true hand. The left real palm felt very cold. He had no conception of where his true left hand was, and for orientation he would feel for it with the right. At this time, squeezing the left leg was felt as though the pressure was applied to the right ankle. At times, he would feel that the left lower limb was flexed at hip and knee, when actually he saw that it was not, and also that the left arm and leg seemed heavier and fatter than the right. On Oct. 23, he felt two false hands, one above the other, both attached to the medial border of the left forearm. This lasted only for a few days. He was dizzy. On Oct. 31, his speech was bulbar, syllabic, and at times difficult to understand. The pupils were equal and reacted well to light. The retinal vessels were arteriosclerotic, and a small hemorrhage was noted to the temporal side of the left disc. There were no gross quadrantic field

defects. The eyes converged well, but left lateral gaze was impaired; right lateral gaze was absent. Upward gaze was impaired; downward movement was fairly well done. There were quick oscillatory movements of both eyes. There were marked right peripheral facial paralysis, slight weakness of the right motor fifth nerve, and a considerable amount of hearing defect on the left. The deep reflexes were diminished on the left. The abdominal reflexes were missing, and there was a bilateral Babinski toe sign. There was considerable awkwardness in the use of the left limbs, particularly the upper. Throughout the left side of the body, all cutaneous sensation was missing, except for slight perception of coldness in the left hand and retention of heavy touch (or pressure) perception on the left sole. Position and joint sense was appreciated at the left knee, shoulder, and elbow. There were no abnormal mental trends.

The condition persisted, more or less unchanged, and on Nov. 26 the patient typed or dictated the following letter:

"Dear Dr. M.: I have been considering your request that I prepare a sketch of the phantom,* or parasitic, or second, hand on my left arm. I find this impractical because my eyes are not sufficiently steady to make such a sketch and because this phantom hand appears to assume many different forms. At first it appeared to be on a section of forearm, 4 to 6 in. long, joined to my real forearm in such a manner that the two hands with their respective forearms formed an angle of some 45 degrees. The phantom hand (palm) faces the back of my real hand. It varies from one-half to the full size of my real hand. Later the phantom hand appeared to have no connection whatsoever to my real arm. This was probably brought about by my assuring myself that no phantom hand existed. I traced the left arm from the shoulder to the fingertips with my good right hand, and I also observed the left arm. By doing this, I was convinced that there was no phantom hand. Usually the phantom, or parasitic, hand appears only in the afternoon and early evening. Invariably, the phantom hand appears behind the real hand; i.e., the palm of the phantom hand faces the back of the real hand, and the interior of the arm feels cold. I use the term interior because I have used the electric heating pad on the arm, warming up the skin until I was fearful of burning it, and still the hand and arm felt cold on the "inside." I have thus convinced myself of two facts: First, the phantom arm or parasitic hand does not exist, and, second, although keeping the regular arm warm tends to prevent the appearance of the phantom hand, no amount of external heat will make it disappear when it does appear. The best treatment I have discovered is, first, to convince myself that there is no phantom hand, and then to take aspirin or Empirin on the assumption that this phantom hand is a neurotic manifestation."

On Nov. 27, 1950, the patient felt that the phantom hand appeared 8 to 12 in. above the left forearm and was not connected with it (illusion of corporeal displacement). He had completely "lost" his own left hand and had to sweep his right hand down from the left shoulder to find his left hand. All postural appreciation was lost below the left shoulder. It was much impaired in the left toes and foot, was slight in the left knee, and was good at the left hip. Pain was lost on the left side. He was unable to move his eyes to the right but had some left lateral gaze. By mid-December the parasitic hand began to disappear and he would go as long as four days without it. The real left hand still felt cold; a "black spot" was clearing up in the left eye; both sides of his mouth and nose felt sore. It was found that there was lack of sensation on the left side of the nose and on the lower quarter of the right side. Some movements at the left shoulder (upward, outward, and inward) were felt. Flexion at the left elbow was appreciated; gross movements of the left fingers and wrist were not. There was general hyperreflexia in the four limbs, with a bilateral Babinski toe sign. Cutaneous sensation over the entire left side was missing. In the lower limbs, there was no appreciation of movements of the left foot and toes; gross movements of the hip and knee were felt.

The patient was admitted to the Neurological Institute on Dec. 4, 1950, for 10 days, under the care of Dr. Carmine Vicale, who furnished the following data: All laboratory data were negative. The electroencephalogram (Dec. 5) was negative. A large central scotoma involved the left eye. There were no quadrantic or hemianopic field defects. No x-ray of the skull or spinal fluid examinations were made.

In February, 1951, he was able to shave himself; his speech was clearer, but there was still numbness about the mouth and nose. He had a variety of symptoms, such as a feeling that he could not open his mouth very far, an itching of the left arm, a peculiar feeling in the left popliteal space, coldness of the left upper extremity, and numbness of the left hand. The physical examination had not changed materially. There was evidence of a left Horner syndrome (a stellate ganglion block had been done on both sides at the New York Neurological Institute). Little or no mention was made of the parasitic member at this time. By April, 1951, the phantom limb

* The term "phantom" as used by the patient was adopted by him after interviews with his physician.

had disappeared. He complained of dizziness, partial loss of vision in the left eye, a sensation of movement of the eyes, an annoying coldness of the left hand and arm, a marked "pins-and-needles" feeling in the left arm and leg, double vision, pain in the left knee and back of the left hip, numbness of the left side of the face, impaired taste and hearing on the left, and a feeling that at times the left upper limb was in an abducted position, when it actually was lying across his chest. The physical signs were essentially those previously noted.

The patient and his family moved to Virginia, and no further medical contacts could be made. In June, 1953, it was learned by mail that he had died, after several "strokes."

Comment.—There seems little doubt about the gross anatomical diagnosis, namely, vascular lesions (thrombotic) in the brain stem, particularly on the right side in the basilar-artery territory. There are a number of interesting points in this case. 1. The patient's clear mentality and insight into the illusory nature of his parasitic hand, and the illusory posturing of the left upper and lower limbs at times. 2. The earlier attribution of the left limb to someone else, a symptom which disappeared, to be followed by the development of the parasitic part. At no time thereafter did the patient deny the presence of his hemiparetic limb, and at no time were there any visual hallucinations. 3. Almost total deafferentation of the affected left limb and left side, together with the feeling of intense cold in the left "hands," i.e., the real and the parasitic hands on the left. 4. The belief that the parasitic left hand initiated and controlled the movements of the real left hand. 5. The absence of any right or left confusion, aphasia, or apraxia. 6. The lack of any clinical or other evidence of cerebral cortical disease. 7. The disappearance of the illusory awareness of the parasitic hand.

There were no evidences of personality abnormalities prior to the onset of this illness. He was a well-integrated and highly intelligent person, who got on well with his family and associates.

CASE 2.—A woman aged 66 had been active and intelligent without antecedent mental illness or personality disorder. She had been mildly hypertensive, 180/90-100, and had been having headaches in the left parietal region for about six months. She was first seen on Aug. 20, 1953. For the week prior to admission the headaches had been continuous and associated with nausea. About 10 days prior to hospitalization she began to scream at times and became temporarily confused. She developed mild weakness in the right hand and some speech disturbance. The neurological examination showed right homonymous hemianopsia on double simultaneous stimulation; at times on the face to hand test sensation would be extinguished in the right hand. There were right lower mimetic facial weakness and mild right hyperreflexia with diminished right abdominal reflexes. She was unable to calculate, and she had lost orientation for right and left. The first examination revealed some bilateral finger agnosia. There was a remarkable body-image disturbance in that she maintained that the examiner's fingers were hers when they were placed in the palm of her hand. This was maintained with her eyes open and closed, and to an equal degree in each hand. She did not regard any other parts of the examiner's body as hers. Thus, the examiner placed his foot on her foot, and she was quick to differentiate her foot from the examiner's. She could never be made to count more than five fingers. There was not the slightest evidence of astereognosis. When she observed one examiner stick a pin into his own fingers, placed in her hand, she admitted that she did not feel it and reluctantly admitted the discrepancy involved in insisting that his fingers were hers. On a reexamination in the course of her illness, she continued to show this curious incorporation of alien fingers into her own body image, but would quickly get irritable, and finally say, "I know you want me to say they are your fingers; so I'll say they are," but it was obvious that she was doing this in order to get rid of the examiner.

The EEG test revealed the presence of a focal lesion in the left parieto-occipital area, and a pneumoencephalogram revealed a space-occupying lesion in the same area. Operation disclosed an irremovable lesion deep in the left temporoparietal region; following operation, right hemiplegia with global aphasia developed.

Comment.—The interest in this case centers about a Gerstmann syndrome, associated with a curiously isolated, externally projected body-image disturbance, for which the patient had no insight. We have no specific data on her premorbid personality, but there was no history of any outspoken abnormalities in her psychic make-up. She did not deny illness in any sense. At no

time did she show any lack of concern; indeed, she was much worried about her illness and its gravity.

It is interesting to speculate upon the relationship of a finger agnosia to the most persistent illusion, involving the incorporation of another person's fingers in her body schema. One might regard this as a remarkable extension of the agnosia into an illusory conception of the parts concerned.

CASE 3.—The patient, a man, was seen at Bellevue Hospital about 10 years ago. He was in the 70's and suddenly developed a left hemiplegia on the basis of thrombosis of the right cerebral blood vessels, due to cerebral arteriosclerosis associated diabetes mellitus and hypertension. The patient denied the presence of left hemiplegia and attributed the left limbs to his son, John. He would lie in bed with his head and body constantly turned to the right. He had a left pyramidal hemiplegia with the usual signs, a left hemisensory defect, and left homonymous hemianopsia. A very curious auditory phenomenon was repeatedly noted. If one approached his bed from the left and spoke to him, he would answer without looking at the speaker and without recognizing the speaker's voice as such. However, the moment one passed the midline of the bed into the right "field," he would say, "Oh, this is Dr. so and so," and his voice would take on a different pitch and tone, almost as if a new person had come into his auditory field. This response was constant and oft-repeated. The nature of this left hemianacusis is of special interest in relation to the other left-sided signs, including the delusional beliefs concerning the identity of his left limbs, which he could not be made to recognize as his under any circumstances. At times this patient presented the picture of an organic mental syndrome with confusion and disorientation.

Comment.—In this case, "denial" reached a high degree, amounting to a left hemiimperception, which invaded even the auditory as well as the motor, sensory, and visual fields. This case belongs to the type decribed by Bender, Wortis, and Gordon.[5]

In a series of 10 cases of anosognosia with denial of impairment in function, we found that all these patients showed severe mental changes and profound defects in visual and cutaneous sensations. The disorder of the body image was present on the left side in 9 cases; the 10th showed the syndrome of denial of blindness. Eight of the patients had a concomitant flaccid left hemiparesis. Mentally they showed retardation, distractibility, fluctuation in performance, disorientation, and poor memory. In the presence of these mental changes, the anosognosia was always limited to that part of the body which showed a defect in function, whereas the patient's responses in the normal regions were always correct. Other features were marked disturbances in the patient's reactions to his outer world. Frequently there were misinterpretations and mislocalizations of objects or people situated in the outer space, but only on the affected side. Observation over long periods revealed a change in the clinical picture. At the onset the anosognosia was absolute and complete. As time elapsed, the patient became less emphatic in the denial of the disturbed functions. There were fluctuation and uncertainty in his responses. Ultimately, when the mental symptoms cleared, he became aware of the defect in his sensory-motor functions. During the period of recovery, a consistent pattern in the anosognosia was noted. The defect was most pronounced in the distal portion of the extremities and the hand was affected more than the foot. These patterns of alteration in function are similar to those noted in cases of other types of disorder in sensation, such as in allesthesia, extinction, and phantom limb.

CASE 4.†—An 83-year-old white widow was admitted to Bellevue Hospital for the first time on March 25, 1935, because of blindness and confusion, of sudden onset. Her history was not judged fully reliable.

Present Illness.—She had evidently been well until between one and three months before admission, when she suddenly experienced dizziness, mental confusion, and bilateral blindness, which lasted for a number of hours and cleared up spontaneously (insufficiency of basilar arterial system). Further episodes of confusion occurred until the day prior to admission, when she again became totally blind, and was admitted to the hospital.

There was no information concerning her previous mental status.

Examination.—Physical examination revealed an elderly white woman in no acute distress. The pulse rate was 92, and respiration rate 18 a minute; the blood pressure was 140/85 mm. Hg; the temperature 98F. There were bilateral varicosities, with brawny edema of both legs. The heart was enlarged to the left. The remainder of the physical examination was within normal limits.

Neuropsychiatric Examination.—She was confused and disoriented, with impaired judgment, memory, recall, and ability to calculate.

She walked on a wide base with short, unsteady steps. Smell was intact. She was blind in both

† Dr. Louis Hausman permitted the report of this case.

eyes, with a complete denial of blindness. The optic fundi were normal. There was no nystagmus. Ocular movements appeared normal. The pupils were round, regular in outline, and reacted to light directly and consensually. Hearing was impaired bilaterally, with air conduction greater than bone conduction.

With double simultaneous sensory stimulation, there was extinction of stimuli on the left. There were no deep or superficial reflex changes.

The EEG showed a grossly and diffusely pathological record, with the greatest defect in the left posterior area.

Course.—Except for hemorrhagic cystitis secondary to catheterization, the course of her illness was uneventful.

She was found to be disoriented for time, place, and person, believing that the date was Dec. 24, 1952. She thought she was on a truck in a street in Greenwich Village, that there were two Bellevue hospitals, and that she was in the downtown branch for "middle-class people who need a rest." She not only denied being blind, as was obvious, but maintained that she had four eyes (pointing to her orbits)—two on each side, one situated on top of the other. She spoke of "one good pair and one bad pair." She had "four arms" and "two belly buttons." Moreover, she believed that she was "two people," (bipartition fantasy); and she named one by her married name, the other by her maiden name. She also confided that she had two families of children (this was not true). As for illness, she denied being sick, saying she was either "just visiting" or "just resting."

There were times when she did not reduplicate or otherwise multiply any part, but she always denied blindness or major illness. She was garrulous, but there was no evidence of aphasia or apraxia. She was unable to make simple calculations, such as multiplying 4 by 6, and at times there was difficulty in distinguishing between the right and left sides; the tendency to reduplication and confabulation seemed to be more definite toward evening. There has been no essential change in her condition over the two months prior to this report.

Comment.—This patient was regarded as having sustained an occlusion of the posterior cerebral arteries due to arteriosclerosis. This case fits in with those described by Weinstein and co-workers. Of interest is the absence of hemiplegia or marked sensory impairment.

Case 5.—A woman of 64 was referred by Dr. Miles Atkinson, of New York, on June 7, 1955. For over 20 years she had been subject to attacks of dizziness, associated with a left-sided hearing defect and tinnitus (Ménière seizures) at irregular intervals. She had also had migraine for many years in her early life, ending at the menopause, at the age of 52. In the preceding four years she had had 18 or 20 attacks, lasting a minute, during which the left hand felt as if it were suspended in space a few feet to the front and to the right of her. The phantom hand was of normal size and was stationary. It was not seen. She became frightened and felt for the real left hand with the right hand, realizing, of course, the illusory nature of the phantom hand. Consciousness was not impaired, nor was there any convulsive movement of any kind.

She said that last year, and again in April, 1956, she had suddenly lost vision in the right eye for a moment.

For about a year and a half, she had noted numbness in the ring and little fingers of both hands, mostly at night, sometimes during the day. Early in 1954 a physician found right homonymous hemianopsia. For many years she had had "indigestion." This consisted of a burning in the pit of the stomach, with a similar sensation reaching up to the "throat," associated with regurgitation.

The neurological examination was strikingly negative, the only positive findings being a lessened swing of the right upper extremity, a small left palpebral fissure, and considerable reduction of hearing on the left. There was no evidence of hemianopsia at this time, and no sensory change. There was no head bruit. Muscle development and reflex activity were normal. All mental functions were intact; there were no gnostic or conceptual disturbances. The heart sounds were normal; the rhythm was regular; the rate 84 per minute. The blood pressure was 130/82. X-rays of the skull were entirely normal.

The electroencephalographic report of Dr. Hans Strauss, dated June 15, 1955, gives the following impression: "This record is normal with the patient awake and superficially asleep and during photic stimulation. At no time is there a significant bilateral difference indicating a focal lesion in either hemisphere.

Comment.—In this instance, the patient had had long-standing Ménière seizures and a long period of migraine (which had ceased at the menopause, a dozen years ago). There were focal seizures apparently consisting of perception of a left phantom hand projected to the right and in front of the body. There was no evidence of a gross focal expanding or vascular lesion. The brevity of the attack and its appearance in a patient with a long-standing history of migraine and Ménière seizures would seem

to stamp the condition as epileptiform. Interest also attaches to the history of a transient right homonymous hemianopsia. The presumed site of the epileptogenic focus is the left parietal lobe.

Comment

In the foregoing case presentations a variety of clinical pictures are described, mainly from a descriptive viewpoint.

Various investigators have attempted to explain the neurophysiology and psychology underlying these unusual manifestations.

As noted in the Table, Critchley has attempted a classification on a symptomatic basis. However, there is an insistent challenge to the neurophysiologist and the psychologist to clarify and categorize the symptoms and signs in terms of disturbed functional patterns. Since Hughlings Jackson described nervous phenomena at successive levels of integration in the neuraxis, this approach has permeated neurological thought and has become very well known. Thus, Orton [6] noted that sensory impulses end in the cortex in what he called the "arrival platform," or first level. Their formulation into concepts takes place on a different psychic plane, in cortical fields, usually situated near the first level. At this second level they become patterned into "knowing" or gnostic "forms" (engrams) capable of recall by the psychic process called memory. Some of these patterns undergo further elaboration at the highest, or third, level to become components of the faculty of symbolic thinking.

In the last quarter of a century, the study of sensation has been carried forward at various levels: by recognition of the body-image functions of the parietal lobes, and by the recent discovery by Magoun [7] of a secondary sensory system at the conducting level, which is concerned with directing attention to the long-described incoming sensory stimuli. Obviously, this "arousal" mechanism has great significance in the phenomenology of consciousness.

Bender [8] has made notable contributions to the "extinction" of various sensations on the affected half or part of various sectors of the body when double simultaneous stimuli are applied. To this recently much-discussed condition the term "perceptual rivalry" has been given.

Recently, Denny-Brown, Meyer, and Horenstein [9] have carried on the Jacksonian tradition in their very detailed and penetrating study of a case of suspected right parietal vascular lesion. These authors believe that sensory reception and perception involve stimulus transmission along (*a*) sensory conduction pathways in an all-or-none response from the periphery to the optic thalamus. At the level of the parietal cortex (*b*) morphosynthesis takes place, based mainly upon spatial summation and discrimination of the incoming stimuli. Apparently, reinforcement and the multiplication of stimuli (recruitment) at this level also play important roles. At this perceptual level, each parietal lobe presides over the opposite half of the body in equal degree. At a still higher gnostic level (*c*) conceptual constellations are organized, and one approaches symbolic thinking, with all its ramifications and effects on motor patterns (praxis) and language (phasia). It is not always easy to define the boundary between complicated perceptual patterns and symbolic formulations, especially since a given patient may show disturbances in both spheres. Obviously, these processes are not only concurrent at times but actually confluent also. It is a question whether this is a matter of much significance in an analysis of so complicated a neural process.

In our first case, one sees disturbance at all sensory levels—from the "lower" conducting to the highest symbolic. (In this connection, one may comment on the fact that our present neurophysiological knowledge merges with and is replaced by psychological data—a necessary but artificial division based on the different techniques presently used by investigators in both fields.) On the other hand, in Case 5, one encounters an epileptiform discharge with no evidence of sensory defect at any level.

To regard the phantom hand of this patient as a disturbance in body schema of very transient nature may well be justified, since there is an extrapersonal projection of a "well-constructed" part of the body. When one considers Case 4, with the phenomena of reduplication of parts of the body and the environment, one must regard the disturbance mainly at the highest level of symbolic formulation, particularly since the mental mechanism of denial is also added. Likewise, when one considers the participation of personality reactions and motivations, as described by Weinstein and his co-workers,[3] one is led to believe that the highest level of cortical activity is involved. When one considers those instances, as in Case 3, in which projection mechanisms come into play, causing the patient to misidentify his paralyzed limb, one again is faced with an added mental aberration which suggests the "triggering" at least of high-level cortical activity.

Concerning the question of denial, which plays an important dynamic role in the cases described, Linn[10] has made some pertinent psychoanalytic observations. He points out that "perception of the outer world weakens denial and interference with perception strengthens it." He believes that some of these patients have a tendency to "inexact perception," i.e., a "studied capacity to use their powers of observation carelessly," which facilitates denial of the signs of illness and helps fulfill the fantasy of well-being. Denial of illness represents "the first stage in a complex system of defense . . . [causing] an attenuation of reality which then facilitates repression," by eliminating those perceptions which would contradict the denial. Repression may also block the perception of specific instinctual demands, thus adding to the denial "potential."

The survey of such a series of cases demonstrates the difficulty of strict categorical placement of the functional disturbances which lead to illusory awareness of body parts in certain instances of cerebral disease.

Conclusions

A personal study of five cases, as well as those described in the literature, shows that disturbances in body image appear in a variety of settings and forms. Some of the syndromes show considerable fluctuation, as in our Case 1. Although there may be profound mental disturbance in some cases, our first, second, and fifth cases did not show an organic mental syndrome or other similar polysymptomatic mental clinical picture of fixed pattern; our Cases 3 and 4 did. Apparently, the basic "denial complex," described by Weinstein and his coworkers, is not always present. Whereas our third case showed a complete pattern of hemidepersonalization (or imperception) and denial, our second case, by contrast, showed an unusual bilateral, fragmentary disorder in perception characterized by incorporation of the fingers of others with her own without any apparent disorder of her own body configuration other than an inconstant finger agnosia. The fourth case, with the phenomena of reduplication, was similar to those described by Weinstein and his co-workers.[3] In the fifth case, the phantom hand seemed to constitute a fragmentary type of epileptiform seizure.

These five cases demonstrate the wide variation of the clinical picture. In the more complex pictures, as in Cases 1, 3, and 4, we seem to be dealing with dynamic disturbances in which the abnormal functioning brain, site of organic disease, exhibits shifting patterns of disorganization, sometimes of transient duration. In these cases, disturbed function is apparently initiated by organic cerebral disease, and involves complex mental mechanisms, which have been explored by the psychoanalyst, the psychiatrist, and the student of organic neurology. The simpler types of dysfunction exemplified by our Cases 2 and 5 are also of great interest.

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Abstracts from Current Literature

Physiology and Biochemistry

EDITED BY DR. BERNARD J. ALPERS

CARBOHYDRATE METABOLISM IN BRAIN DISEASE: VI. LACTATE METABOLISM AFTER INFUSION OF SODIUM D-LACTATE IN MANIC-DEPRESSIVE AND SCHIZOPHRENIC PSYCHOSES. M. D. ALTSCHULE, D. H. HENNEMAN, P. HOLLIDAY, and ROSE-MARIE GONCZ, A. M. A. Arch. Int. Med. 98:35 (July) 1956.

The authors studied the metabolic dysfunction in various so-called functional psychoses. In this instance a follow-up on previous observations concerning accumulations of abnormal quantities of blood lactic acid following dextrose administration to schizophrenic patients is made by injecting sodium lactate intravenously and noting the rate of disappearance of this substance from the blood of psychotic as well as of other groups of patients. A significant lag in removal of blood lactate following such injection is noted in schizophrenic patients, and this lag is to some degree proportional to the severity of the psychosis, for example, patients whose condition was considered to be sufficiently recovered to warrant discharge failed to demonstrate this lag. In no case, however, was the delay in disappearance of lactate commensurate with that noted in patients with liver disease or such anoxic states as cardiac decompensation, anemia, pulmonary disease, etc.

PARSONS, Montrose, N. Y.

MICRODETERMINATION OF PHOSPHOLIPIDES AND SPHINGOLIPIDES IN BRAIN. E. ROBINS, O. H. LOWRY, K. M. EYDT, and R. E. MCCAMAN, J. Biol. Chem. 220:661, 1956.

Methods for the determination of cerebral lipids have formerly required 50 to 1000 mg. of tissue. Robins and co-workers have now developed methods for measuring cephalins, lecithins, total sphingolipids, sphingomyelins, non-phosphorus-containing sphingolipids, and total phospholipids in a single 10γ dry-weight sample of brain.

PAGE, Cleveland.

DISTRIBUTION OF LIPIDES IN THE CEREBELLAR CORTEX AND ITS SUBJACENT WHITE MATTER. E. ROBINS, K. M. EYDT, and D. E. SMITH, J. Biol. Chem. 220:677, 1956.

The granular cortex of monkey brain contains the least amount of lipid in the three layers, chiefly due to densely packed nerve cell bodies in this layer. Non-phosphorus-containing sphingolipids are present in very low concentration in the molecular layer and in somewhat higher concentration in the granular layer. Gangliosides probably account for the higher values in the latter. Cerebrosides are in low concentration in both layers of the cortex. The suggestion is made that cephalins are as characteristic of white matter as are cerebrosides, cholesterol, and sphingomyelin.

PAGE, Cleveland.

BIOCHEMISTRY OF THE SPHINGOLIPIDES: IX. CONFIGURATION OF CEREBROSIDES. H. E. CARTER and Y. FUJINO, J. Biol. Chem. 221:879, 1956.

Psychosin (galactosidosphingosine) has been obtained in good yield from alkaline hydrolysis of phrenosin. Reduction yields dihydropsychosin, which on hydrolysis gives an excellent yield of erythrodihydropsychosin. No threo-isomer could be found among the hydrolysis products. Thus the sphingosin moiety of phrenosin has the erythro-configuration.

PAGE, Cleveland.

LAMINAR MICROELECTRODE STUDIES OF SPECIFIC SOMATOSENSORY CORTICAL POTENTIALS. CHOH-LUH LI, C. CULLEN, and H. H. JASPER, J. Neurophysiol. 14:111 (March) 1956.

Analysis of evoked potentials at measured depths in the somatosensory cortex of the cat was carried out by microelectrodes, recording the action-potential spikes from single cortical cells (intracellular or extracellular). The surface-positive phase of the classical

evoked potential is represented by a higher-voltage negative local potential of 5-10 msec. when recorded extracellularly in Layer IV, where specific afferent terminals and Golgi Type II cells are numerous. It is felt that this potential results from summated depolarization of presynaptic afferent terminals and is amplified by the Golgi cells. The surface-negative phase of the evoked potential showed a potential decrement as the electrode is inserted beneath the surface of the cortex and is reversed in Layers IV and V. It probably represents a wave of depolarization propagated over ascending apical dendrites following transynaptic activation of large nerve cells in the depth of the cortex.

Cortical cells close to specific afferent terminals fire with the shortest latency (1-2 msec.) following single shock to thalamic sensory nucleus, these units probably being monosynaptic.

The latency of unit responses may be reduced with an increase in the intensity of the thalamic shock. This results in a reduction in repetitive discharge, so that with maximum stimulation the unit may fire only once at the peak of the potential, suggesting inhibitory influences at high intensities of stimulation.

SIEKERT, Rochester, Minn.

THE INSULA: FURTHER OBSERVATIONS ON ITS FUNCTION. W. PENFIELD and M. E. FAULK JR., Brain 78:445:1955.

Penfield and Faulk report their findings in stimulation of the insula during craniotomies under local anesthesia with an intragastric rubber balloon attached to an electrogastrograph. This enabled Penfield and Faulk to study the effects of stimulation and extirpation of the insula in man upon the motor activity of the stomach.

Electrical stimulation in four of six cases produced effects which varied from complete inhibition of gastric motility to the production of violent activity with marked increase in tone. Whenever abdominal sensation was produced by stimulation during gastric recording, there was some concomitant change in gastric tone or motility, producing either inhibition or acceleration of gastric motility. Motor effects, however, were occasionally produced without accompanying sensation. The authors question whether abdominal and epigastric sensation have any representation in the insula independent of the changes produced in motility and tone of the gastrointestinal system.

When the insula was removed, the normal 3-per-second contractions of the pylorus were inhibited and there was a decrease in gastric tone. In control studies of gastric motility during similar operations, when other parts of the cerebral cortex were stimulated, there was no evidence of gastromotor activity.

More than one-third of the sensory responses to stimulation of the insula consisted of an abdominal feeling which was assumed to be secondary to motor changes in the gastrointestinal tract.

MANDEL, Philadelphia.

CONTRIBUTION TO PATHOGENESIS OF NEUROMUSCULAR ATROPHY. L. VAJDA, Monatsschr. Psychiat. u. Neurol. 130:422, 1955.

Vajda reports the case of a 32-year-old woman with neuromuscular atrophy, studied by muscle and peripheral-nerve biopsy and creatine-creatinine metabolism. Significant histological changes included proliferation of the endo- and perineurial connective tissue, with integrity of vascular elements but without perceptible overgrowth of Schwann cells. An infiltration of the perineurium with fibroblasts, lymphocytes, and plasma cells was observed. In the muscle itself, there was noted a heterogeneous mixture of intact, atrophic, and hypertrophic fascicles, with aggregations of central and hypolemmal nuclei. Original studies of the arteriovenous levels of creatine-creatinine of specific muscles before and after movement revealed a marked rise in postcontraction venous creatine levels involving atrophic muscles, thereby suggesting an initial elimination of creatine, rather than creatinine, occurring in affected muscles during contraction.

PARSONS, Montrose, N. Y.

RING BINDING OF SKELETAL MUSCLE. R. E. PERRY, A. G. SMITH, and R. N. WARREN, A. M. A. Arch. Path. 61:450 (June) 1956.

Ring binding of skeletal muscle was encountered in 4 of 58 biopsies. The muscles on which biopsies were made were all from the lower extremities, and the ages of the patients, all male, ranged from 15 to 41 years. The youngest patient suffered from

bilateral flexion deformities of the fourth and fifth fingers, bilateral spastic pes planus, and rigid feet; there was moderate atrophy of his calves. The other three specimens were obtained, respectively, from a case of peripheral neuropathy of unknown cause, a leg amputated because of arteriosclerotic vascular insufficiency, and a case of chronic osteomyelitis of the left femur. Ring binding was observed as the occurrence of circular, complete, or incomplete bands, averaging 8μ in width and extending circumferentially around muscle fascicles. The bands had distinct cross striations and were within the sarcolemma of the fascicle; they stained as muscle with the Masson technique. Occasional complex forms were seen in which the constrictions ran through, as well as around, the fascicles. Based on the premise that these bands represent a state of spastic contraction of the involved muscle, attempts were made to reproduce them in mice and guinea pigs by the injection of strychnine. Occasional bands were seen in the control group, but none were found in the test animals. The authors believe ring binding represents an abnormal change of skeletal muscle due to contracture or hypertonicity, and that it is not pathognomonic of a specific disorder. They believe that the bands arise as a result of buckling and spiraling of the outermost fibers of the fascicle around a core of spastic, contracted muscle.

APONTE, Philadelphia.

Psychiatry and Psychopathology

PSYCHOSIS APPARENTLY PRODUCED BY RESERPINE. H. A. SCHROEDER and H. M. PERRY JR., J. A. M. A. 159:839 (Oct. 29) 1955.

Schroeder and Perry describe psychotic behavior with agitated depression occurring in five patients receiving reserpine, with complete recovery when the drug was discontinued. Such behavior had not been known in these patients prior to taking this drug.

ALPERS, Philadelphia.

AN ATYPICAL FORM OF PHENYLPYRUVIC OLIGOPHRENIA. W. KEUP, Monatsschr. Psychiat. u. Neurol. 129:344 (April) 1955.

A patient with most of the typical features of phenylpyruvic oligophrenia, including mental deficiency, characteristic dental configuration, and pigmentation, was subjected to a phenylalanine test. On the basis of obtaining urinary levels of phenylpyroracemic acid above normal, and yet somewhat below values customarily obtained in this syndrome, the author postulates a relative insufficiency of the enzyme system (phenylalanine oxidase and coenzyme diphosphopyridine) essential to the complete degradation of phenylalanine. It is further postulated that such formes frustes as express themselves in the above-mentioned metabolic alterations are characterized by corresponding degrees of the other stigmata of the affection.

PARSONS, Montrose, N. Y.

Meninges and Blood Vessels

TYPHOID WITH MENINGITIS (SALMONELLA TYPHOSA): REPORT OF CASE IN INFANT WITH RECOVERY. S. M. POWELL, A. M. A. J. Dis. Child. 91:380 (April) 1956.

Powell reports on an infant with S. typhosa meningitis, a rare affliction. No gastrointestinal symptoms, petechiae, or nuchal spasm was present, but fever, upper respiratory tract infection, and, later, convulsions occurred. Chlortetracycline, intravenously, and streptomycin, intrathecally, were used. The spinal fluid was purulent and contained 750 mg. of protein per 100 cc. and 45,000 lymphocytes per cubic millimeter.

SIEKERT, Rochester, Minn.

TUBERCULOUS MENINGITIS IN CHILDREN. G. BOYD, A. M. A. J. Dis. Child. 91:477 (May) 1956.

Boyd's present treatment of tuberculous meningitis in children is as follows: (1) Streptomycin, 0.5 gm. twice daily, intramuscularly, for three months, then every second or third day up to six months. (2) Isoniazid, 10 mg. per kilogram of body weight daily, orally, in two doses 12 hours apart, for three months; then 5 mg. daily for three months; then 2.5 mg. daily for 12 to 18 months. (3) Daily ventricular aspiration in patients with high intracranial pressure, usually necessary for only 7 to 10 days. Since this regimen

was adopted, 40 patients have been treated, without a death. Early diagnosis and its difficulties are noted.

SIEKERT, Rochester, Minn.

ROLE OF ATLANTOID COMPRESSION IN THE ETIOLOGY OF INTERNAL CAROTID THROMBOSIS. E. BOLDREY, L. MAAS, and E. MILLER, J. Neurosurg. 13:127 (March) 1956.

Boldrey and his associates report a clinical review of 24 cases of angiographically demonstrated occlusion of the internal carotid artery, all of which were assumed to be caused by thrombosis. Thirteen of the patients were in the fifth decade of life, indicating a higher incidence of internal carotid artery thrombosis than usual for this age group. As in other reported cases, the most frequent initial complaint was hemiparesis or paralysis on awakening in the morning. In five instances convulsions preceded the hemiplegia. Headache or head pain was found in all but four cases, the pain being orbital, retro-orbital, or occipital in location. Two patients had diabetes, and two had thromboangiitis obliterans. Eleven patients had clinical evidence of peripheral vascular thickening. Two patients had injuries before the onset of symptoms; these could not be correlated with the thrombosis.

The authors describe a right hemiparesis, right hemianopsia, and aphasia in a 47-year-old woman which occurred while she gazed to the right and which cleared within five minutes. Four days later the same symptoms recurred, with left temporal and left retro-orbital pain. A left carotid arteriogram revealed absence of filling of the internal carotid artery opposite the lateral process of the atlas. At operation, the carotid artery was found to be adherent to the lateral process of the atlas and to move with the atlas when the head was turned. There was also a purplish discoloration of the vessel, confined to the point of contact of the vessel with the atlas.

Numerous theories have previously been reported to explain internal carotid artery thrombosis. The authors believe that an extraneous factor is present to account for the large number of "spontaneous" thromboses of the internal carotid artery. The internal carotid artery, in its ascent in the neck, bears a close relationship to the lateral process of the atlas so that when the head is turned to the right or left, the carotid artery lies directly upon this process. Adhesions in the carotid sheath are frequently associated with this relationship of the atlas, and this may account for a number of cases of "spontaneous" carotid artery thrombosis, either by mechanical compression or by vasospasm. In some instances this mechanism may be a contributing, rather than a primary, one.

When clinical evidence suggested transitory compression of the carotid artery, surgical amputation of the lateral process of the atlas resulted in improvement or relief of the underlying situation.

MANDEL, Philadelphia.

SOME FACTORS INFLUENCING THE NONVISUALIZATION OF THE INTERNAL CAROTID ARTERY ANGIOGRAPHY. N. H. HORWITZ and R. H. DUNSMORE, J. Neurosurg. 13:155 (March) 1956.

Horwitz and Dunsmore report four cases in which there was nonvisualization of the internal carotid artery by angiography. In each case the patient was moribund and in deep coma at the time of angiography and increased intracranial pressure had occurred precipitously. Although the pathological process in all instances was not the same, the rapid rise in intracranial pressure produced brain stem compression, which undoubtedly accounted for the state of in extremis presented by each patient. The failure to attain sufficient dye concentration could have been related to alterations in the cerebral blood flow. Some degree of vascular disease was also present in each case. Compression of the diencephalon may also have initiated a neural reflex which altered the intracranial circulation so as to make its visualization impossible. These factors must be considered in order to distinguish them from the picture seen in thrombosis of the internal carotid arteries in the neck.

MANDEL, Philadelphia.

SUBARACHNOID HEMORRHAGE: PROGNOSTIC FACTORS. R. H. DUNSMORE and J. L. POLCYN, J. Neurosurg. 13:165 (March) 1956.

The authors reviewed 81 cases of spontaneous subarachnoid hemorrhage in which no diagnosis of ruptured aneurysm could be made. The mortality was about 27%. When

it was not possible to demonstrate a causal lesion, the prognosis from the standpoint of hemorrhage was good, and if the patient survived the subarachnoid hemorrhage for a year, the prognosis was excellent. There was no predilection for any age group, although most of the patients were 20 to 60 years of age. There was no major difference in age groups of which survived and those which died.

Of the 52 survivors, 3 had recurrent hemorrhage and lived up to five years after the recurrent hemorrhage. Presumably, these patients were felt by the authors to have had berry aneurysms that were either microscopic or unlocalizable by angiographic techniques. The etiologic factors in these subarachnoid hemorrhages were not clear, but they were assumed to represent aneurysms that had developed sufficient clot to prevent their filling at angiography. Others could not be visualized because of their position or because of technical difficulties.

MANDEL, Philadelphia.

Diseases of the Brain

RENAL DISEASE, INNER EAR DEAFNESS AND OCULAR CHANGES. E. SOHAR, A. M. A. Arch. Int. Med. 97:627 (May) 1956.

Sohar describes a new heredofamilial syndrome consisting of nephritis, alterations of the ocular lens, and nerve-type defects occurring in four male siblings, with evidence of transmission through the maternal line. The lenticular defects consisted of posterior cataract and spherophakia, the latter condition representing a mesodermal maturation defect associated with brachydactyly, etc.

PARSONS, Montrose, N. Y.

CEREBRAL AQUEDUCT STENOSIS. J. GREENWOOD JR. and W. C. HICKEY, Dis. Nerv. System 17:277 (Sept.) 1956.

Greenwood and Hickey report eight cases in which stenosis of the aqueduct was treated surgically by the insertion of an indwelling rubber catheter through the stenosed aqueduct. This aqueduct-cisternal shunt was accomplished and provided relief of internal hydrocephalus over long periods of time. In one case of stenosis secondary to arachnoiditis the patient survived 22 years. The authors believe that a rubber tube is superior to polyethylene tubing except where an extremely small caliber is desired. The fact that rubber maintains its integrity was substantiated in the case which survived for 22 years.

This procedure, because of its simplicity, should in some instances be considered over other shunt procedures which are now being used.

MANDEL, Philadelphia.

DIAGNOSTIC ERRORS DUE TO HIGH SPINAL FLUID LEUKOCYTE COUNT IN SUBDURAL HEMATOMA. W. E. SCHATTEN and F. E. NULSEN, J. A. M. A. 159:559 (Oct. 8) 1955.

Schatten and Nulsen report on two cases of subdural hematoma in which elevated spinal fluid leukocyte counts led to an erroneous diagnosis of meningitis. They emphasize the fact that the leukocyte count of the cerebrospinal fluid is not, by itself, diagnostic of meningitis and should not prevent exploratory trephination of the skull when a growing mass is suggested by progressive deterioration of sensorium. Because of the insidious behavior of the subdural hematoma, even a temporary misdirection in the management of such a case as probable meningitis can result in death, while complete recovery can be achieved by early surgical intervention.

ALPERS, Philadelphia.

ROLE OF THE RETICULAR FORMATION IN THE COMA OF HEAD INJURY. E. L. FOLTZ and R. P. SCHMIDT, J. Neurosurg. 13:140 (March) 1956.

The changes in the electrical activity of the brain following head injury are characterized by depression of the cortical electrogram and even greater depression of activity from the medial reticular formation. The central region in the cephalic tegmentum is concerned with consciousness, and, since this region receives impulses from the classical sensory pathways, it is presumed that this continuous sensory bombardment "drives" the reticular activating system, thereby maintaining the conscious state. Reduction in this sensory impact results in spontaneous sleep, from which the subject may be aroused by an appropriate increase in the sensory output. When this sensory "drive" is abolished, coma occurs.

The authors produced acceleration concussion injuries of the brain experimentally in monkeys and noted that the sensory-evoked responses in the reticular formation were selectively absent. The responses in the lemniscus recorded at the same time were absent. Since unconsciousness is the single criterion for cerebral concussion, since loss of sensory activation of the reticular formation results in unconsciousness, and since these conditions were produced simultaneously, the authors concluded that the unconsciousness produced by concussion is the result of a sudden loss of sensory activation of the brain stem reticular formation.

Clinically, this finding may account for the unconscious state following head injuries and occasional negative findings after trephination when subdural hematomas are suspected.

MANDEL, Philadelphia.

"POLYCYTHEMIA" ASSOCIATED WITH CEREBELLAR HEMANGIOBLASTOMA. A. A. WARD JR., E. L. FOLTZ, and L. M. KNOPP, J. Neurosurg. 13:248 (May) 1956.

Polycythemia rubra vera frequently produces central nervous system symptoms, and cases have been reported previously of the association of polycythemia with posterior fossa hemangioblastomas.

The authors report two cases of cerebellar hemangioblastomas (solid type) in which pre- and postoperative peripheral blood counts and blood value determinations revealed that the increased red blood cell count, hemoglobin, and hematocrit were caused by an increase in erythrocytic elements only and that following the surgical removal of the tumor these values were sharply decreased. This picture was seen only in the solid type of hemangioblastoma, and not in the cystic type. The authors theorize that solid hemangioblastomas secrete a hormonal factor, which exists in sufficient concentration to produce erythropoesis, but that the cystic hemangioblastomas lack secretory tissue, explaining perhaps the absence of polycythemia vera in cystic tumors. Further experimental studies will be necessary to prove this hypothesis.

MANDEL, Philadelphia.

PINEALOMA WITH METASTASES IN THE CENTRAL NERVOUS SYSTEM. F. D. FOWLER, E. ALEXANDER JR., and C. H. DAVIS JR., J. Neurosurg. 13:271 (May) 1956.

The authors report three cases of pinealoma in which metastases occurred within the central nervous system by way of the cerebrospinal fluid. Tumors of this type have been classified frequently as teratomas and have often been found to metastasize within the central nervous system.

Because of the poor results obtained by surgical removal in the past, the best method of treatment is considered to be relief of increased intracranial pressure by ventriculocisternostomy and irradiation of the posterior portion of the third ventricle. The potent effect of radiation was demonstrated in two of the authors' three cases, in which the tumor could not be removed completely by surgery but, following a course of radiation therapy, no evidence of tumor was found at autopsy.

In view of the spread of pineal tumors via the cerebrospinal pathways, the authors advocate total irradiation of the central nervous system through the multiple-port technique prior to the appearance of metastatic lesions. Adequate treatment should be given to the region of the third ventricle, the suprachiasmatic structures, and the cauda equina, as they are the most frequent sites of metastasis in the central nervous system.

MANDEL, Philadelphia.

LONG-TERM FOLLOW-UP OF 106 CASES OF ASTROCYTOMA, 1928-1939. ARTHUR R. ELVIDGE and A. MARTINEZ-COLL, J. Neurosurg. 13:318 (July) 1956.

The survey of Elvidge and Martinez-Coll was based on a total of 112 cases of astrocytoma which occurred over an 11-year period, with a long-term follow-up in 90% of the cases. Six tumors were omitted, as two of these were glioblastoma multiforme, one a intramedullary cyst without available sections, and three unclassified malignant astrocytomas. Of the remaining 106 tumors, 53 were piloid astrocystomas, 29 were astrocytoma diffusum, and 24 were gemistocystic astrocytomas.

In the group of astrocytoma diffusum, the average age of the patient at the time of admission to the hospital was 33 years, with approximately equal distribution between the sexes. Epilepsy was the first symptom to occur in 62% of the cases, with focal

seizures occurring more commonly than generalized seizures. Of the 29 tumors, 27 were located in the cerebral hemispheres and 2 in the third ventricle, but none was found in the cerebellum. There were 7 operative deaths, and 19 patients were available for follow-up study. Seven of these patients died within the first year after operation; one died five years after operation, and eight survived for more than eight years. As in most cases the tumor could not be removed completely surgically, partial removal followed by x-ray therapy proved to be the most effective method of managing these cases. Three cases in this group were unavailable for further study.

Gemistocystic astrocytomas were found in the cerebral hemispheres and third ventricle, with epilepsy occurring as a presenting symptom in 45% of the cases. Among the 24 cases in this group, there were 6 operative deaths within the first week and 1 death three months after operation. Of the 18 surviving patients, 5 died within the first postoperative year; 5 survived less than 3 years, and 8 survived 4 to 10 years after operation. The patients with the longest average postoperative survival after complete removal were those who had the earliest surgical treatment. Cysts occurred most frequently in this group.

Of the cases of piloid astrocytoma, epilepsy was found in 75%. The average postoperative survival in 20 cerebral hemisphere cases was 7 years, while in the 14 cerebellar cases the average postoperative survival period was 13 years. When the tumor was in the third ventricle or the basal ganglia, the average postoperative survival was one year four months. In the group of 20 cerebral hemispheral tumors, 8 were cystic, whereas in the cerebellar group, of 14 cases, 9 were cystic. In the 12 cases of noncystic tumors the average survival period was 3.8 years, whereas postoperative survival in the 9 cystic cerebellar tumors was 16.5 years.

MANDEL, Philadelphia.

CEREBELLAR SOFTENING. B. FAIRBURN and L. C. OLIVER, Brit. M. J. 1:1335 (June 9) 1956.

Fairburn and Oliver report three cases with clinical manifestations indicative of a space-occupying lesion which was caused by softening and swelling of one cerebellar hemisphere, probably due to vascular occlusion. In such cases they advise immediate decompression of the posterior fossa.

ECHOLS, New Orleans.

INTRASPINAL EPIDERMOID TUMORS. C. CHOREMIS and others, Lancet 2:437 (Sept. 1) 1956.

Choremis and his co-workers describe six cases of pearly tumors (cholesteatoma or epidermoid tumors) in patients whose ages ranged from 7 to 12 years of age. All of these children had been successfully treated two to seven years earlier for tuberculous meningitis. These writers believe that the two conditions are closely related. They postulate that repeated lumbar puncture may implant epithelial cells which in time form these tumors.

YASKIN, Camden, N. J.

THE PARKINSONIAN SYNDROME. K. HARTMANN, Monatsschr. Psychiat. u. Neurol. 129:92 (Jan.-March) 1955.

Hartmann reports a series of 552 cases of Parkinsonism from the standpoint of differential diagnosis of paralysis agitans and postencephalitic and arteriosclerotic Parkinsonism. These three forms constituted about 98% of the series (14%, 60%, and 24%, respectively), the remaining 2% being accounted for by cerebral syphilis, brain tumors, and poisoning with carbon monoxide and manganese. The review was prompted by a survey of the author's data, some of which suggested recent change in the course and symptomatology of Parkinsonism from that previously described and generally accepted. Some of the deviant findings included the following: Significant numbers of cases diagnosed as paralysis agitans exhibited relative predominance of rigidity (as contrasted with tremor); a relatively high incidence of a fine tremor occurred as a first symptom in certain cases of postencephalitic Parkinsonism (those in which sleep disturbance had been minimal or absent), and relatively frequent disturbances of seborrheic secretions were noted in the cases of paralysis agitans (as contrasted with postencephalitic Parkinsonism, where the reverse was observed, despite the otherwise high incidence of autonomic disturbances in this condition). The variability of the symptomatology of the several postencephalitic syndromes is stressed, and the author emphasizes the fact that

some of the features classically associated with postencephalitic Parkinsonism, such as the ocular crises, the prominence of rigidity, the rapid development and course, and the vegetative manifestations, are characteristic sequelae only of the form of encephalitis associated with sleep disturbance (some 54% of the "postencephalitic" types); these features are often not encountered where this has been absent. The author comments on an interesting inverse correlation noted between the response to drug therapy and the prominence of autonomic involvement in all cases of Parkinsonism.

PARSONS, Montrose, N. Y.

STUDIES OF CRANIOCEREBRAL DYSRAPHIAS: II. AGENESIS OF THE CEREBELLAR VERMIS; MEDIAN RHOMBOCEPHALIC DYSRAPHIA. G. DE MORSIER, Monatsschr. Psychiat. u. Neurol. 129: 321 (April) 1955.

Among the differential diagnoses of the syndrome produced by space-consuming lesions of the posterior fossa is to be included "rhomboschizia," a rare malformation, which, when complete, involves agenesis of the cerebellar vermis and the adjacent medullary paraolivary area, including the dorsal accessory olives and much of the spinocerebellar pathways. The defect, while present throughout life, may attract clinical attention in adulthood. Dr. Morsier describe two fatal cases occurring in infants under 2 months of age. Autopsy findings revealed the malformation to be partial in one instance and complete in the other.

.. PARSONS, Montrose, N. Y.

TIME, NEUROLOGICALLY CONSIDERED. B. SCHLESINGER, Monatsschr. Psychiat. u. Neurol. 129: 354 (April) 1955.

Schlesinger considers defective appreciation of time from the standpoint of perception, memory, and thought. Disturbances in awareness of time include lengthening and shortening, as well as obliteration, of the subjective time scale and panoramic experience (concentration of the subjective time scale) and are to be regarded as forms of selective impairment of consciousness. Disturbances in appreciation of time involving recollection include retrospective lengthening and shortening of the subjective time scale, as well as time-lapse paramnesia (rapid memory flow during mental stress), reverberating paramnesia (perseverative memory flow occasionally induced by drugs), and the déjà vu phenomenon. These conditions are to be regarded as forms of memory disturbance. Finally, phenomena such as reduplicative paramnesia (where an original experience is mistaken for a recollection) or cryptamnesia (where a recollection is identified as an original experience) and many instances of retrospective falsification of the time scale constitute manifestations of mental confusion wherein disturbances of memory or thought or both are present. The author postulates the involvement of the medullary reticular activating center; the medial nuclear complex of the thalamus, the prefrontal lobes, and the posterior associative cortex as necessary for the differentiation of engrams essential for temporal patterning of behavior.

PARSONS, Montrose, N. Y.

Diseases of the Spinal Cord

IDIOPATHIC PAROXYSMAL MYOGLOBINURIA. L. REINER, N. KONIKOFF, M. D. ALTSCHULE, G. J. DAMMIN, and J. P. MERRILL, A. M. A. Arch. Int. Med. 97:537 (May) 1956.

Among the metabolic diseases producing red urine and neurological disorders may be named idiopathic paroxysmal myoglobinura. The syndrome is characterized by the acute onset of muscle pain; cramps, progressing on occasion to convulsive seizures, and paralysis of the lower extremities, associated in most instances with chills, anorexia, vomiting, epistaxis, tachycardia, abdominal pain, and renal involvement. Predominant pathological lesions have consisted of necrosis of skeletal muscles and lower-nephron nephrosis. The diagnosis may be established by the demonstration of myoglobinuria and by skeletal muscle biopsy. Included in the differential diagnosis of idiopathic paroxysmal myoglobinuria are acute porphyria, paroxysmal hemoglobinuria and march hemoglobinuria, muscular dystrophy, myasthenia gravis, dermatomyositis, and myotonia dystrophica, as well as secondary myoglobinuria, such as in cases of crush injuries of skeletal muscles, carbon monoxide poisoning, and high-voltage accidents. The authors report two cases and review the literature extensively.

PARSONS, Montrose, N. Y.

Peripheral and Cranial Nerves

LESIONS OF PERIPHERAL NERVES DEVELOPING DURING COMA. C. W. OLSEN, J. A. M. A. 160: 39 (Jan. 7) 1956.

The unique aspect of peripheral nerve involvement in coma is the combination of mononeuritis, due to pressure or vascular spasm, and polyneuritis, due to anoxia. This syndrome is not limited to the coma of carbon monoxide intoxication but is also seen in coma due to drug intoxication.

In four instances of prolonged coma caused by intoxication with carbon monoxide, barbiturates, natural gas, and acetylsalicylic acid, flaccid paralysis and other symptoms of damage to peripheral nerves were combined in various ways with spasticity, transient hemiparesis, and other signs of damage to the central nervous system. Chronic alcoholism with malnutrition should be considered as a possible contributing factor in such cases.

ALPERS, Philadelphia.

GENESIS OF POSTOPERATIVE BRACHIAL PLEXUS LESIONS. F. JELASIC, Monatsschr. Psychiat. u. Neurol. 129:461 (May) 1955.

Experience with four cases of transitory postoperative brachial plexus affections induced the author to study 100 normal human subjects exposed to maintenance of various arm positions encountered during surgery. The duration of exposure before development of symptoms and/or signs of brachial plexus involvement was carefully noted. The critical position was that of 90-degree abduction, aggravated by hyperextension ("dropping" below horizontal plane when supine) and assumption of the Trendelenburg inclination. Within one hour of sustained abduction approximately two-thirds of the subjects developed changes suggestive of brachial plexus dysfunction, and in over one-half of these subjects first subjective complaints occurred within 30 minutes, to be followed by objective sensory disturbances and, finally, by motor signs (in about one-sixth of the affected subjects). Distal involvement was characteristic, with median and ulnar combinations most frequently encountered. The critical minimum and maximum intervals for the development of lasting palsy were estimated to be 30 and 60 minutes, respectively, from the time of appearance of first motor signs, thus suggesting the considerable unlikelihood of this complication as a consequence of unphysiological positioning of the arms in surgical procedures lasting less than one hour and the necessity for suitable precautions in procedures having a duration of over 90 minutes.

PARSONS, Montrose, N. Y.

Vegetative and Endocrine Systems

ADRENAL PHEOCHROMOCYTOMA SIMULATING DIABETES INSIPIDUS. F. TEVETOGLU and CHI-HAO LEE, A. M. A. J. Dis. Child. 91:365 (April) 1956.

Tevetoglu and Lee report on an 8-year-old boy with a pheochromocytoma who presented with polydipsia and polyuria. He could concentrate his urine only to a specific gravity of 1.005. The authors briefly review 47 cases from the world literature, 6 with a history of polyuria and polydipsia.

SIEKERT, Rochester, Minn.

Treatment, Neurosurgery

POSTDIPHTHERITIC POLYNEURITIS AND PSEUDODIPHTHERITIC POLYNEURITIS: REPORT OF 2 CASES TREATED WITH CORTISONE AND CORTICOTROPIN. H. J. ROBERTS, A. M. A. Arch. Int. Med. 97:618 (May) 1956.

Roberts reports two cases of postdiphtheritic neuropathy treated with hormones. In one instance, in which fairly definite laboratory evidence of diphtheria was noted, the systemic infection was succeeded after two to three weeks by the development of a rapidly progressing motor weakness involving palatal and ciliary musculature, which gradually responded to cortisone and corticotropin over the next month. Bacteriologic studies of the second patient failed to confirm the diagnosis of diphtheria. However, the clinical picture was suggestive. Some two weeks following severe pharyngitis, the above train of neurological symptoms appeared and progressed rapidly over the first

week. Within 24 hours following the administration of cortisone (coincidentally in the treatment of urticaria, considered to be a reaction to penicillin), the neurological involvement regressed to a full remission. The differential diagnosis of diphtheritic polyneuritis includes other causes of polyneuritis, such as porphyria, infectious mononucleosis, intoxications, and the conditions responsible for the Guillain-Barré syndrome. Differentiation from acute bulbar poliomyelitis is essential.

PARSONS, Montrose, N. Y.

AN INVESTIGATION OF NEUROSURGICAL ALLEVIATION OF PARKINSONISM, CHOREA, ATHETOSIS, AND DYSTONIA. I. S. COOPER, Ann. Int. Med. 45:381 (Sept.) 1956.

The failure of medical therapy to halt the progress of Parkinsonism has led neurosurgeons to devise destructive operations upon the nervous system in order to alleviate the symptoms of this disease. Such operations have included resection of the premotor cortex, pyramidotomy of the spinal cord, and section of the pyramidal tract in the cerebral peduncle; and, more recently, the stereotactic apparatus has been used to produce destructive lesions in the basal ganglia.

Cooper reports 200 operations which were performed upon patients suffering from Parkinsonism, chorea, athetosis, and dystonia musculorum deformans. Fifty-five of these operations consisted of surgical occlusion of the anterior choroidal artery, and 145 operations of chemopallidectomy.

The rationale for occlusion of the anterior choroidal artery is that infarction occurs in the mesial portion of the globus pallidus and certain of its extrapyramidal neural connections. The operation of chemopallidectomy involves the placing of a small polyethylene catheter through a trephine opening in the skull into the medial portion of the globus pallidus and injection of a solution of 95% alcohol in 8% celloidin. This results in immediate alleviation of contralateral tremor and rigidity.

The operation of anterior choroidal artery occlusion was found to be best suited for young patients with postencephalitic Parkinsonism of long duration and great incapacitation. By means of this operation, the contralateral tremor and rigidity of Parkinsonism were relieved in 70% of the 55 cases. The gait was improved in a number of cases, for in some instances patients who were previously bedridden prior to surgery were able to walk. Deformities of the hand improved after this procedure. The operative mortality as a result of anterior choroidal artery occlusion was 10%.

In the operation of chemopallidectomy, 70% of 125 patients had a pronounced alleviation of contralateral tremor for lasting periods. The mortality rate was 3%, and hemiparesis occurred in four patients.

Cooper emphasizes the careful selection of cases for this operation, for elderly patients must be able to withstand the procedure under local anesthesia. Patients with advanced muscular weakness or severe mental changes should not be selected for the operation.

MANDEL, Philadelphia.

MANAGEMENT OF PURULENT MENINGITIS. J. N. ETTELDORF, J. A. M. A. 159:750 (Oct. 22) 1955.

Failures in management of meningitis have been attributed (1) to failure to establish an early clinical diagnosis; (2) to inadequate laboratory facilities for accurate and rapid identification of the etiological agent, and (3) to lack of necessary discrimination in the selection and use of therapeutic agents.

If the diagnosis of meningitis is established early and followed promptly by an intense and adequate therapeutic and supportive treatment, the mortality and undesirable sequelae of this disease will be minimized. Early recognition of the complications followed by energetic treatment also has an important place in the management of this disease.

ALPERS, Philadelphia.

DEPRESSION AND ANXIETY OCCURRING DURING RAUWOLFIA THERAPY. J. C. MULLER, W. W. PRYOR, J. E. GIBBONS, and E. S. ORGAIN, J. A. M. A. 159:836 (Oct. 25) 1955.

A severe mental illness developed in 7 (7.5%) of 93 patients receiving Rauwolfia for periods of 2 to 12 months. Of 28 patients, 2 (7%) developed this illness while receiving a crude root preparation, Raudixin, and 5 (7.7%) of 65 patients while taking the purified alkaloid, reserpine. The mood disturbance was primarily depression in two patients,

depression with anxiety in three patients, and anxiety state in two patients. Suicidal tendencies were present in two patients. A history of previous psychiatric illness was obtained from five of the seven patients. It is thus suggested that therapy with Rauwolfia extracts may trigger or precipitate a mental illness in somewhat unstable patients already predisposed. All patients in this series received reserpine in dosage relatively large as compared with that currently recommended.

Two of the seven patients responded to reassurance and supportive therapy. Five patients required electric shock therapy. The response was good for three patients and fair for two patients.

The authors emphasize the potential severity of this complication arising during Rauwolfia therapy. Caution in Rauwolfia administration is recommended, with particular reference to total daily dosage and to previous psychiatric history.

ALPERS, Philadelphia.

TRIGEMINAL NEURALGIA: TREATMENT BY SURGICAL DECOMPRESSION OF POSTERIOR ROOT. R. D. WOOLSEY, J. A. M. A. 159:1713 (Dec. 31) 1955.

The decompression procedure of Taarnhj will relieve trigeminal neuralgia. Woolsey carried out this operative procedure on 45 patients with severe trigeminal neuralgia. No patients died. Twenty-one, or about one-half, have had some hypesthesia on the involved side. This has lasted three to six months. Forty-two patients have had complete and lasting relief of pain for two months to three years.

In this series of 45 patients, 3 had temporary minor paralysis of the fourth nerve. These paralyses cleared within six months. Temporary paralysis occurs about as frequently after this decompression procedure as after section of the trigeminal nerve. One of the three patients with peripheral paralysis of the seventh nerve responded well to cortisone. The other two responded poorly. In the patient who appeared to be benefited the paralysis cleared completely in two weeks.

Woolsey feels it is too early to be able to say how many patients undergoing such decompression will have to be subjected to nerve-root section for final relief of pain. Until the procedure can be finally evaluated, the decompression procedure seems preferable to nerve-severing techniques. The Taarnhj procedure is the surgical procedure of choice in persons presenting neuralgia of the ophthalmic division, whether a recurrence following differential section or a primary neuralgia of the ophthalmic branch. Parasthesias found in nerve-severing techniques are absent in this procedure. Neuroparalytic keratitis is avoided, and this point is of particular importance in persons with primary ophthalmic-branch involvement.

ALPERS, Philadelphia.

FURTHER EVALUATION OF ACETAZOLEAMIDE (DIAMOX) IN TREATMENT OF EPILEPSY. C. T. LOMBROSO, D. T. DAVIDSON JR., and M. L. GROSSI-BIANCHI, J. A. M. A. 160:268 (Jan. 28) 1956.

Acetazoleamide (Diamox), by inhibiting the carbonic anhydrase throughout the body, causes profound metabolic changes and affects the acid-base balance of blood and body fluids. It was administered by mouth in a series of 126 patients with various forms of epilepsy. Treatment extended for periods of from three months to three years.

In 37% of cases seizures were reduced by at least 90%, in 17% they were reduced 50% to 90%, and in 46% they were reduced by 50% or less. None were made worse, nor was any serious side-effect or abnormality of blood, urine, or bone encountered. The degree of improvement was not related significantly to a personal history of brain damage, a family history of epilepsy, or the type of seizure. Benefit was greatest for patients having 3-per-second spike-wave discharges of the electroencephalogram. Maximum benefit occurred if the alkalosis induced by hyperventilation of the lungs resulted in maximal increase of spike-wave discharges and of "build-up" in the record. In some patients, well controlled for at least three months with therapy, seizures later returned. Reinstitution of therapy with the drug later often produced the initial favorable response.

ALPERS, Philadelphia.

DIPHENYLHYDANTOIN (DILANTIN) SODIUM USED PARENTERALLY IN CONTROL OF CONVULSIONS. J. T. MURPHY and R. S. SCHWAB, J. A. M. A. 160:385 (Feb. 4) 1956.

Since the preparation of the original solution of diphenylhydantoin (Dilantin) sodium for parenteral use, in 1950, a total of 9710 doses have been administered. There are no

local side-effects from the intramuscular or intravenous injection of this preparation. The general effects are similar to those in oral administration of the substance.

This preparation was successfully used to prevent seizures in neurosurgical operations and to stop those that seemed to be beginning. It was also used in the treatment of status epilepticus, and its effect on the central nervous system was nonsedative and nondepressant.

ALPERS, Philadelphia.

CONTROL OF CHRONIC PAIN BY *dl*-ALPHA ACETYLMETHADOL. N. A. DAVID, H. J. SEMLER, and P. R. BURGNER, J. A. M. A. 161:599 (June 16) 1956.

The analgesic effect of racemic α-acetylmethadol was studied in 49 patients suffering from chronic pain due to cancer, 10 recovering after surgery, and 17 in chronic or transient pain from other causes. Doses of 5 to 10 mg. given three or four times daily, were highly effective on continued use.

Good relief from pain was obtained by either oral administration or subcutaneous injection. Hypnotics were usually needed for sleep. It was possible in several patients to discontinue use of frequent injections of large doses of morphine or meperidine and to change over completely to the oral use of acetylmethadol without causing withdrawal symptoms.

With large daily doses (30 to 50 mg.) of acetylmethadol, constipation was bothersome. A few patients complained of lethargy, usually during early use of the drug and when using larger doses than necessary. Relatively long duration (four to five hours) of analgesic effect was obtained from single oral doses of acetylmethadol during the first two or three months of its trial. However, the eventual development of tolerance and, more likely, the progressive deterioration of the patient shorten this prolonged action and necessitate an increase in dosage. The authors believe that slow cumulation of the drug explains the continued analgesic effectiveness and prolonged action of acetylmethadol when given orally; however, cumulation leading to severe toxic effects may occur if too large doses are used or account is not taken of the patient's metabolic and excretory status.

In the majority of patients in this series the oral administration of acetylmethadol afforded relief from chronic pain for several months without severe untoward effects.

ALPERS, Philadelphia.

News and Comment

ANNOUNCEMENTS

The American Board of Psychiatry and Neurology, Inc.—The following candidates were certified by the American Board of Psychiatry and Neurology, Inc., at a meeting of the Board in New York, Dec. 10 and 11, 1956. Supplementary certification is indicated by an asterisk (*) preceding the name.

NEUROLOGY

Austin, James Henry, Portland, Ore.
Cook, Robert E., San Francisco
*Douglas, Donald B., New York
Ehmke, Bruce Carlyle, Peoria, Ill.
*Goldstein, Norman Philip, Rochester, Minn.
Kempinsky, Warren H., St. Louis
Mandel, Martin M., Philadelphia
Moossy, John, New Orleans
Parsons, Thomas C., Montrose, N. Y.
Sibley, William Austin, Cleveland
Skillicorn, Stanley A., San Jose, Calif.
Stevens, Janice Robinson, Portland, Ore.
Tentler, Robert L., Chicago
Tucker, Howard Jerome, New York

SOCIETY NEWS

Congress of Neurological Surgeons, Inc.—The sixth annual meeting of the Congress of Neurological Surgeons was held at the Palmer House in Chicago, on Nov. 1, 2, and 3, 1956.

At this meeting Dr. Frederick C. Rehfeldt, of Fort Worth, Texas, assumed the presidency. Dr. R. K. Thompson, of Baltimore, was elected vice-president. Dr. Irwin Perlmutter, of Miami, Fla., and Dr. John R. Williams, of Grand Rapids, Mich., were elected to the executive committee.

The seventh annual meeting of the Congress of Neurological Surgeons will be held at the Statler Hotel in Washington, D. C., on Nov. 7-9, 1957.

American Academy for Cerebral Palsy.—The American Academy for Cerebral Palsy held its 10th annual meeting in Chicago (headquarters at Congress Hotel) Nov. 17, 18, and 19, 1956.

The officers for the forthcoming year are Dr. Nicholson J. Eastman, president, Baltimore; Dr. William T. Green, president-elect, Boston; Dr. Raymond R. Rembolt, secretary-treasurer, Iowa City.

The 1957 meeting will be held in New Orleans, Nov. 25, 26, and 27, at the Roosevelt Hotel.

Books

Blakiston's New Gould Medical Dictionary. Edited by Normand L. Hoerr, M.D., and Arthur Osol, Ph.D. Price, $11.50. Pp. 1463, with 252 illustrations on 45 plates, 129 in color. The Blakiston Division, McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1956.

The quickly expanding vocabulary of medicine demands that an up-to-the-minute medical dictionary be available to the profession. The 1956, second edition of the "New Gould Medical Dictionary," which comes so soon on the heels of the 1949, first edition seems admirably to fill a pressing need. The rapid expansion of all fields of medicine, and hence the need to define new words and to redefine others, is expressed in the 12,000 new terms and 8000 changes in this second edition.

This edition has a more rigid cover than its predecessor, and the finger index has been altered so that all the letters face the front cover for ease of word finding. Two members of the editorial board of the first edition are the editors-in-chief for this edition: Norman Hoerr, M.D., and Arthur Osol, Ph.D.

There are approximately 20 tables which are new or which have been appreciably changed. One in the Appendix, describing radioisotopes that are commonly used in medicine, presents the type and energy of radiation, the radioactive half-life, and the medical uses of the radioisotopes. Tables classifying Parkinson's disease, personality types, leukemias, types of penicillin, and viruses are added. The list of viruses in this edition is about twice as long as in the previous edition. The 45 illustrative plates have been published unchanged from the first edition. Plate 17 remains one of the clearest illustrations of the base of the brain and its circulation yet published.

One finds new words from the fields of pharmacology, psychiatry, immunology, and nuclear science with ease, and this mirrors the progress of medicine in these fields. Several of the newer ataraxic drugs are listed by generic and trade names. Words such as cortisone, Salk, radioisotope, and passive-aggressive personality, not present in the first edition, appear in this one.

As is usual, the definitions of various medical terms will not be agreed upon by all. The definition of *anosognosia* is perhaps too restrictive. Spellings in this edition are accurate. The word *syntonic* (listed under personality types), which was misspelled in the first edition, has been corrected in this one. This "New Gould Medical Dictionary" represents the culmination of a monumental effort by its 88 contributors from the various specialties of medicine.

Emotional Hazards in Animals and Man. By Howard S. Liddell, Ph.D. Price, $2.50. Pp. 97. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

This work is a readable and instructive monograph. Though included in a series known as "American Lectures in Objective Psychiatry," it is more accurately described as a study in comparative behavior. Some aspects of the total behavior of the subjects, chiefly goats, sheep, and a few pigs and horses, have been quantitatively recorded and compared with man.

It is implied that the behavior of the animals studied is easier to understand or more readily interpreted than the behavior of man. How doubtful is this inference is shown by the following example: It is suggested that the conditioning experience is traumatic for most adult animals and especially for a young animal separated from its mother. Hence, situations were designed to establish whether, and for what period of time, kids separated from their mother goats are injured by the conditioning experience. It was shown that the behavior of kids so exposed was disturbed for long periods. For explanation, the author then calls upon the widely shared impression that a mother exerts a protective and instructive influence during the period of development and that in the absence of the mother the kid is less well prepared for life. This is anthropomorphizing in modern terms.

Also, he draws a striking inference about the long-term effects of adverse early experience from the early death of one such animal "conditioned" in the absence of

its mother. It would be extremely important, and in keeping with contemporary opinion about adverse situations in man in relation to health, if it could be shown unequivocally that a series of animals so deprived during the early period of their living have a shorter life span than their more privileged litter mates.

Also, the author sometimes suggests how an animal views a situation confronting it. Hunches of this sort may be legitimate, but they are no more devoid of the possibility of error in the case of the goat than in the case of man. Unfortunately, the reading of contemporary notions about human motivation into behavior patterns of domestic animals does not greatly enrich our understanding of human phenomenology.

The words "fear," "pain," and "acute emotional experience" are introduced to illuminate animal behavior patterns and abreactions in terms of what these words mean in human experience. Studies of situations which involve "loneliness," "monotony," "confusion," and "overstimulation" nicely demonstrate that such factors also operate in the lives of goats. The effects of too rapid and excessive learning pressures on horses again simulate what is observed in some humans, but the data here, as in other instances in the essay, are anecdotal.

Praise and admiration are due the author for his patience, for his affection for his "subject," and for his efforts in understanding barnyard behavior. He emphasizes the need for the naturalist's point of view in studying animal and human behavior, and for being just as inventive outside the laboratory situation as within it in assessing the effects of a given experience.

This little book is warmly recommended. It affords delight and illuminates the process of the true naturalist at work.

The Yearbook of Modern Nursing. Edited by Cordelia M. Cowan. Price, $4.50. Pp. 446. G. P. Putnam's Sons, 210 Madison Ave., New York 16, 1956.

The first edition of "Yearbook of Modern Nursing" contains discussions of present-day nursing concepts, as well as references, digests, and bibliographies. This book has been prepared by leading educators in nursing and allied fields and should be useful to physicians and surgeons who serve on nursing school councils and advisory committees, in addition to being valuable to nurses in preparing teaching programs.

The selections on Neurological Nursing and Psychiatric Nursing are well presented and have excellent bibliographies.

Masked Epilepsy. By Hugh R. E. Wallis. Price, $2.50. Pp. 51. E. & S. Livingstone, Ltd., 16-17 Teviot Pl., Edinburgh 1, 1956.

This short book, of 51 pages, can be read in one to one and a half hours. The theory is advanced that in children episodes of abdominal pain, vomiting, pyrexia, headache, sleep disturbances, somnambulism, and behavior disorders may be various forms of seizure disorders. There are 31 case reports in the book. Sixteen patients (about 1% of new patients seen by the author between 1951 and 1954) are described as having "masked epilepsy," i. e., manifestations of seizures other than those of convulsions or unconsciousness.

The flurry of controversy surrounding this subject is reflected in several references to other workers' criticism of the author's premise. The author answers these criticisms in a very direct manner, but, owing to the small number of observations made and the difficulty which often exists in proving the existence of a seizure disorder, many of these answers are undocumented. The opinion that headaches, sleep disturbances, and certain behavior disorders may actually be the seizure, rather than a reaction to having a seizure disorder, appears particularly controversial.

The book has value in focusing attention on the diverse forms which seizure disorders may take.

Classics of Biology. By August Pi Suner. Price, $7.50. Pp. 337. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1955.

This work is an important review of changing attitudes in biologic science written by the distinguished Spanish biologist August Pi Suner. The attitudes he reviews are extremely relevant to medicine and to those interested in the function of the nervous system.

To many energetic and creative physicians the question "Has disease meaning?" seems fatuous and woolly. Mindful of the hard-won battle necessary to establish the experimental method and attitude in medicine, they are loath to recognize questions about meanings and goals. Indeed, from the middle of the nineteenth century until recently, the study of parts and elements has been pursued so intensively and, incidentally, so successfully as almost entirely to consume the energies and interest of creative minds. Thus, the study of man in the context of his environment was considered an unsuitable subject for science. Attempts to gain a more inclusive view were not compatible with that period's genius. It is evident that each period has its own particular insight and preferred kinds of knowledge. The history of thought has been characterized by swings in interest from the whole to the part and then to the whole again.

As a matter of fact, antedating the lively interest in part-phenomena of the past four decades, Claude Bernard, the great French biologist of the early nineteenth century, did not hesitate to ask "Has disease meaning?" Indeed, he saw disease as the outcome of attempts at adaptation to noxious forces. These responses, though appropriate in kind, he saw to be faulty in amount. He suggested that the adaptive response, in its intensity, could be more destructive than the original assaults, and that an individual might be damaged gravely through the wrong magnitude of his defensive reaction. For instance, the presence of micro-organisms in the lung evokes cellular and humoral responses that serve to meet invasion and do so effectively. Yet the magnitude of the responses may lead to congestion of the lungs and pneumonia. The provocative effect of the scope and simplicity of this thesis cannot be overestimated.

However, Claude Bernard's emphasis upon experiment initiated the swing toward intense preoccupation with the kind of questions which designed experiments can answer, and hence the growth during the next period of the study of part-phenomena.

With the unfolding of the twentieth century, the need for unifying knowledge and for the study of relationships among parts again was voiced in many areas of thought and effort. In medicine during the century's first quarter there was a reaction against extreme partitioning of inquiry. It was J. S. Haldane, the distinguished British physiologist, in his now classic monograph on respiration, who said, "Since the time of Hippocrates, the growth of scientific medicine . . . has been based on the study of the manner in which . . . the human body expresses itself in response to change in environment, and that only through the study of it can we recognize and interpret disturbance of health."

Professor Suner does not include Walter B. Cannon in his review, but it was in the first half of the twentieth century, at Harvard, that the latter profoundly influenced thinking by offering a unifying theory concerning the body's drive to maintain internal stability. In other than biologic fields, the contemporary imagination's appetite for unity was being strikingly shown in the major styles in the plastic arts, in the physicist's concept of the continuity of matter and energy, and in the efforts of philosophers.

Many who lived and worked through this period of change shared the growing restiveness of medicine with its own successes. One could see as well its pressing needs. Moreover, Claude Bernard's brilliant definition of disease as resulting from attempts at adaptation deals mainly with primitive biologic levels of reaction. Whereas these hold for man, disease in man has a more complex meaning, since his attempts at adaptation involve a highly developed nervous system. With his elaborate brain he is so constituted that he reacts not only to actual assault but to threats and symbols of danger experienced in his past which call forth reactions, like those to assault. Also, man's special relation to man introduces another set of factors. Hence, backed by long bedside experience and the realization that much of medicine is the understanding of human motivation, physicians in scattered centers throughout the world turned energies into studies of man in his context and the pertinence of this relationship to disease. Enthusiastic about the new wave of interest in purpose and goal, they became convinced that the scientific method was suitable for such study and could be applied. They were challenged by the opportunity, on the one hand, of keeping medicine compassionate and, on the other, of making it even more scientific and dynamic.

It is noteworthy that naturalists, and, more particularly, zoologists, have long by preference and training, and with delight and profit, observed living creatures in their context, attempting to understand their goal-directed behavior. This preference of the

naturalists and their point of view is appraised amusingly by Suner: While physiologists, says he, built their science by means of designed experiments, biologists built theirs by observing the experiments of Nature. Designed experiment divides phenomena into small sections of space and time. Naturalists, on the contrary, freely observe the course of life on a big scale.

So, too, can one see man, his behavior and his diseases, as would a naturalist—one who delights in observing living creatures in their context and attempting to understand their goal-directed behavior.

Suner has written a remarkably interesting summary of these matters, reviewing historical controversies and including quotations and extracts of the writings of an impressive roster of the great students in biology. This book is of interest not only to the physician and scientist but to the thoughtful general reader as well.

Treatment of Migraine. By John R. Graham, M.D. Price, $4.00. Pp. 149. New England Journal of Medicine, Medical Progress Series. Little, Brown Company, 34 Beacon St., Boston 6, 1956.

John R. Graham's little book, entitled "Treatment of Migraine," is an eminently clear and readable account of the clinical phenomenology and therapy of migraine headaches. The author discusses, in successive chapters, the diagnosis of migraine, the dynamics of the migraine attack, treatment of acute symptomatology, prophylaxis, and surgical measures for the relief of headache.

In the last chapter, the difficult and seldom-discussed problem posed by migraine status is comprehensively reviewed. A detailed bibliography and index conclude the volume. The concept that migraine is, in part, a cranial vascular consequence of a way of life is admirably presented, and the discussion of therapeutic agents, especially ergotamine tartrate, is complete and specific. In the consideration of headache prophylaxis, however, the role of the physician-patient relationship and the beneficial effects of alterations in attitude, goals, and values might have been more strongly emphasized.

The author's experiences, cited generously throughout the volume, illuminate his presentation and are the principal charm of the book. The volume should be a helpful guide to all who encounter this exceedingly common disorder.

Mental Illness

A Survey Assessment of Community Rates, Attitudes, and Adjustments

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Currently, much time and effort is being expended in various activities designated as having to do with mental health, without adequate information regarding the bases on which these activities depend. As one example, treatment facilities—clinics, hospitals, etc.—are created and expanded without a great deal of knowledge about the actual number of definable emotional difficulties present within a given community. As another, educational campaigns on many levels are actively encouraged without real attempts to ascertain the basic understanding possessed by the persons who are being exposed to such efforts and without follow-up on the resultant effects.

On the question of the need for facilities, Leighton [1] has estimated that 37% of adults in a community "are psychiatric cases"; Selective Service statistics and other surveys indicate that many persons who are emotionally ill, by existing diagnostic criteria, are not under treatment in mental health facilities. Unfortunately, exact data of this sort are very rare. As to the value of educational programs, Ridenour says flatly [2]: What criteria do we have as to the effectiveness of our educational techniques? The sad answer is: None to speak of. The amount of wishful thinking which goes on with respect to educational methods is appalling.

The study reported here is an attempt to come to grips with some of the problems mentioned above. Admitting the magnitude of the project, the difficulties inherent in a field in which definitions are often unsatisfactory and areas poorly delineated, and the obvious limitations of the method used, we nevertheless have tried to determine some of the public attitudes and practices relating to mental illness and to estimate the amount of diagnosable mental illness existent in a population sample. The survey findings relating to child-rearing practices have been reported elsewhere.[3]

Method

This survey was conducted in Salt Lake City, the capital of Utah and the Mormon mecca of the world. About one-half the population of the city embraces the Mormon religion: patriarchal, home-centered, with an ecclesiastical organization that influences all living activity—political, social, and otherwise. In terms of applying this set of data to any other area in the country, this fact must be kept in mind, since it may introduce a special bias.

The sampling itself was done on a geographical basis, with eight separate blocks arbitrarily selected as fairly representative of a cross section of the population in the city. This expectation was borne out in checking the distribution of the sample

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according to age, education, income, and occupation. Within each geographical area, 25 consecutive families, starting with the home at the northeast corner of a given block, were interviewed without omission; a total of 200 families were included within the sample. Of these 200 families, 175, or 87.5% (comprised of 609 persons of all ages), cooperated fully.* Initially, each family received a personal letter requesting their cooperation, followed by a telephone contact arranging an appointment in the home at the convenience of the family.

The interviews were conducted by a third-year psychiatric resident (N. J. C.) and a psychiatric social worker with several years' experience in adult psychiatric work (O. S.). In labeling psychiatric entities, only overt symptomatology or overt admission of illness was accepted. At the risk of failing to list some cases, subtle and debatable phenomena were ignored, and the raters used only such obvious material as appeared when one subject asked an interviewer if she "brought a special message from the Lord" or another announced that "one-half of his body was pure electricity." Where the examiner could not feel certain of a diagnosis, no labeling was given. With children below the age of 16 years, no diagnosis was given because of the difficulty in separating developmental problems from actual emotional disease.

Incidentally, we might mention also that in the introductory letter to the families, the interviewers were identified with a medical research project, associated with the University of Utah College of Medicine, with no particular identification with psychiatry. This, we feel, reduced guarding to a minimum. Further, the questions were presented in a personal interview setting, rather than as a check list of items. In the beginning, impersonal questions were asked about various aspects of medical care and child-rearing methods, with gradual encouragement of personal commentary and eventual extension into the psychiatric field. Generally, we used clinical examples, such as, "If an adolescent boy of yours were involved in stealing a small sum of money from a gas station, what would you consider the cause and what would you feel should be done?" There was a minimum of "loading," such as occurs when one presents multiple choices.

One other significant factor might be mentioned briefly. As might be expected, the person most frequently available within the home was the wife or mother. Therefore, of the 175 families interviewed, 122 respondents were the wife only, 11 the husband only, and 39 both husband and wife, with a daughter as respondent in 2 instances.

The majority of the respondents were female, and it might be expected that the descriptions of the absent members of the family (whose "mental illness" was diagnosed solely on reported data) depended more on psychopathology in the interviewed members than on actual psychopathology. This is, of course, a justifiable criticism; it is only partly countered by the care taken to exclude all questionable material.

Incidence of Mentally Ill Persons

Of the 175 families who cooperated with the project, 85, or 48.6%, were found to contain one or more persons identifiable as mentally ill. Table 1 indicates which members of the family were mentally ill; the apparent high incidence of illness among the wives may be due to the fact, already mentioned, that the housewives were usually the persons at home and consequently were usually the ones interviewed. At any rate, a total of 111 persons were identified as having definitive mental illness.

Since most of the households contained an average of 2 adults, we can assume that the total number of adults represented in the sample was about 350. With 111 identified as mentally ill (as previously noted, no diagnosis was made for any person under the age of 16, whatever the described behavior), approximately one-third of the total adult sample, roughly equal to Leighton's estimate of 37%,[1] was represented.

TABLE 1.—*Distribution of Illness in Members of Family*

Number	People Ill Within Home Setting
28	Husbands
62	Wives
10	Sons
8	Daughters
1	Grandmother
1	Family relative other than above, in home setting
1	Other than relative, living in home
111	Total

*Though the 25 families who were listed as "uncooperative" would obviously be a sufficiently large group to distort the sample, it was the opinion of the interviewers that their inclusion would probably raise, not lower, the incidence of discernible mental illness reported in this paper. In one group of nine "uncooperative" persons on whom incidental data were available, six were found to be disturbed to a considerable degree.

TABLE 2.—*Categorization of Illnesses Found*

Number	Classification of Illness
11	Schizophrenia (irrefutable delusions, etc.) and involutional states of psychotic proportions
18	Hysterical symptoms: paralyses; polysurgical patients; stuttering, etc.
41	Definitely anxious persons unable to cope with problems; phobias; decompensating compulsions
14	Alcoholism
11	Suicide gestures; other "acting-out" symptoms of severe proportions
6	Senile psychoses or other organic psychoses
10	Psychosomatic illnesses: ulcerative colitis, asthma, ulcer, etc.

Table 2 shows the classification of illness among the 111 persons. Further examination of this distribution and comparison of these figures with those reported by Hollingshead and Redlich [4] justify some comment. In both surveys the greatest amount of illness (of all sorts) was concentrated in the lower economic and social groups. While differences in method make direct comparisons difficult, it was found in the present survey that four-fifths of the families in the lower social strata contained at least one mentally ill member, while less than one-half of the upper-stratum families were thus affected. In the Hollingshead survey, it was found that the psychoses tended to be proportionately greater in the lower-level families, whereas the psychoneuroses were proportionately greater in the upper-level families. Our findings are somewhat at variance with these; in our survey, the psychoses appear to be distributed fairly evenly across the entire social range, with the psychoneuroses approximately twice as frequent in the lower-level families as in the upper levels. (Psychophysiologic reactions tend to be more frequent in the upper levels; "acting-out" types of aberrations, in the lower.)

The disparity between these figures may be due to the difference in the methods of collecting data and leads to an interesting speculation. Since Hollingshead's data were gathered on patients actually under treatment, it may be that the persons with psychoneurotic reactions in the lower-level families simply do not come into psychiatric facilities for treatment. There is a strong suggestion in our findings that they either handle their problems themselves or seek help from extramedical sources.

TABLE 3.—*Type of Treatment Received*

Number	Type of Treatment
30	Medical care of some type
9	Psychiatric care
4	Medical, then psychiatric care
1	Quasimedical treatment (chiropractors, food faddists)
17	Self-treatment, with recognition of self as ill
50	No treatment (no change), no recognition of illness

Treatment

As to the amount of treatment received, 68, or 61.3%, received no treatment whatever through medical channels. Of those who did receive treatment, by far the greatest number received medical care alone; less than half that number received psychiatric care alone or in addition to their medical care (Table 3).

It is worth noting that 17, or 15%, recognized that they were ill and took some sort of definitive measures on their own, drawing on their own resources to aid them in a return to health.

TABLE 4.—*Advice Given a (Hypothetical) Disturbed Neighbor*

Per Cent	Treatment Advised	
35.8	Seek medical aid, including psychiatric help	64.2%
44.7	Take a trip; join a club; get out more, etc.	
15.4	No opinion	
2.4	Do nothing	
1.7	Seek religious assistance	

For example, a woman who had been profoundly depressed, and probably psychotic, following her husband's death reported that she had been a vagrant for two to three years, recovering only when she was suddenly made keenly aware that she had a responsibility to help a neighbor who was in distress.

As a further check on the attitude toward treatment for emotional difficulties, the respondents were given a hypothetical example of a neighbor, known to be overmeticulous in her housekeeping, who gradually developed nameless fears, in-

creased seclusiveness, and, finally, complete inability to leave her home. They were then asked to describe what sort of advice should be given her. Their answers are summarized in Table 4. In this group, 35.8% recommended aid through medical channels; the remainder (64.2%), environmental changes or religious help or expressed uncertainty. This figure closely coincides with the actual behavior of mentally ill people—38.7% did seek such help.

Orientation to Mental Illness

About two-thirds of the persons could admit having had some experience with mental illness somewhere in the family. However, in spite of fairly strenuous educational and informational campaigns in the area, 61.1% knew of no facility to which they might turn for help with a psychiatric problem (Table 5).

There was considerable attempt to sample attitudes regarding mental illness. For one example, 73.7% (Table 6) felt there was a difference between "mental illness" and a "nervous breakdown." Most frequently, the difference was described as follows: A nervous breakdown was considered to be due to outside stresses impinging on the individual, while mental illness was a mysterious "something" inside. The first was curable, most frequently through environmental manipulation; the other, incurable, needing medical attention and, presumably, custodial hospitalization. It seems obvious that the polite term "mental illness" now replaces the ignominious word "insanity" in the public vocabulary. Clausen [5] comments that preliminary reports from a survey by the National Opinion Research Center (as yet unpublished) indicate that laymen think of the "stereotype of the acutely disturbed psychotic whenever 'mental illness' is mentioned and . . . employ mechanistic and naïvely empirical cause-effect schemata in attempting to explain such illness."

As to the possible causes for (undefined) mental illness, Table 7 indicates the responses to questions such as, "Do you feel . . . could be (or is significant as) a cause of mental illness?" There was a distinct, though probably undocumentable, impression on the part of the interviewers that the persons in the lower social groups tended to be much more accepting of the idea that emotions were important; the upper-level respondents could say the proper phrases, but without the affect found in the other answers. As one interviewer put it, "It's as though the upper classes know the words, but the lower can sing the music." When the actual responses, as they appear in Table 7, are correlated with the educational and economic levels of the respond-

TABLE 5.—*Knowledge of Local Psychiatric Facilities*

Per Cent	Knowledge of Local Psychiatric Facilities
61.1	Knew of no facility
22.8	Knew of one or more agencies affiliated with psychiatry
8.1	Knew of a specific doctor, specializing in psychiatric field
8.0	Knew of both doctors and agencies affiliated with psychiatry

TABLE 6.—*Differentiation of "Mental Illness" and "Nervous Breakdown"*

Number	Per Cent	Opinion of Interviewed
129	73.7	Felt mental illness differed from "nervous breakdown"
32	18.4	Felt there was no difference
13	7.4	Did not know
1	0.5	Rejected question

TABLE 7.—*Opinions on Possible Causes for Mental Illness*

Causes of Mental Illness	"Yes," %	"No," %	No Opinion, %
Head injuries	88.8	6.8	4.4
"Change of life"	71.0	17.4	11.6
Heredity	70.0	21.7	8.3
Money troubles	57.5	34.0	8.3
No love in childhood	56.5	29.2	14.3
Not enough will power	55.8	22.5	21.7
Drinking (alcoholism)	52.8	37.3	9.9
A religious punishment	21.7	68.4	9.9
Hard work	21.2	72.0	6.8
Being around insane people	19.8	66.4	13.8

TABLE 8.—*Estimate of "Seriousness" of Clinical Examples*

Opinion of Condition	Paranoid Example %	Neurotic Example %
Serious	50.4	46.3
Relatively normal	35.0	39.0
No opinion	5.6	14.7

TABLE 9.—*Estimate of Causes of a Specific Mental Illness*

Paranoid Example

Per Cent	Cause of Condition
35.8	"Mentally ill, neurotic"
16.4	"Crazy, off his rocker, bats in belfry"
10.1	"Wife is giving him a bad time; lousy boss at work; trouble somewhere with somebody"
9.9	"Everybody has a right to their own little peculiarities"
9.4	"He's got a guilty conscience, that one"
7.8	"Beats me"
3.8	"Somebody is drunk again"
3.1	"Sounds like the green-eyed dragon bit him"
1.5	Multiple factors given
1.5	"You do odd things when you aren't well; he'd better see his doctor"
0.7	"What an imagination!"

ents, no significant differences were found among the various groups.

To check these attitudes further, the respondents were given two clinical descriptions, one of an assaultive, disturbed, floridly paranoid man who burst into a neighbor's living room and accused him of "spying"; the other, previously mentioned, of chronically meticulous neighbor who gradually developed fears of leaving her home. In a deliberately unstructured conversation, the interviewer attempted to estimate to what degree the respondent considered each condition "serious." The results, as estimated by the interviewer, appear in Table 8.

Though we considered the example of the paranoid man almost too dramatic, it is noteworthy that some 35% of the people regarded the condition as "relatively normal." Further, Table 9 bears out this impression of deliberate casualness, with roughly 52% definitely labeling the example as mentally ill and the remainder taking refuge in assorted statements indicating acceptance of the problem. Somewhat the same attempts at normalizing deviant behavior were noted by Yarrow et al.[6] in investigations of the attitudes of wives toward the illness of their hospitalized psychotic husbands.

Summary

Using a personal-interview, largely unstructured approach, trained interviewers visited 200 consecutive homes in eight city blocks in Salt Lake City. In an informal, friendly way, they elicited information regarding the incidence of mental illness or gross emotional disturbance in each family, the attitudes toward mental illness and its treatment, and impressions as to the respondents' sophistication toward possible causes of mental illness and the community resources available for handling such patients.

Within the obvious limitations of the method used, roughly one-third of the adult population sampled in this survey appear to have some kind of specific mental illness, and about one-half the families sampled contain at least one mentally ill person. Of this group, essentially three-fifths receive no medical or psychiatric treatment. Essentially three-fifths of the sampled population knew of no available facility. And essentially three-fifths would not advise a person recognized as mentally ill to seek medical help. One might speculate that factors may be operating which cause these people to resist the acquisition of adequate orientation in this general area, since the degree of naïveté is apparently independent of social, educational, or economic status. In any event, if medical treatment be regarded as the optimum method of handling emotional disorders, broader educational campaigns would seem to be indicated. On the other hand, since it appears unlikely that adequate numbers of clinical facilities will become available in the predictable future, it might be useful to investigate further the nonmedical methods by which many of these mentally ill people are able to keep themselves at some sort of functioning level.

Department of Psychiatry, University of Utah College of Medicine (4).

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Methacholine Test and Epinephrine and Arterenol Excretion

Hemodynamics of Methacholine Test and Its Relationship to Excretion of Epinephrine and Arterenol (Norepinephrine) in Normal and Schizophrenic Subjects

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Funkenstein, Greenblatt, and Solomon[1,2] have published a prognostic test for the selection of neuropsychiatric patients for electric shock treatment. In essence, the test consists of administering 10 mg. of methacholine (Mecholyl) chloride intramuscularly and observing the systolic blood pressure for 25 minutes. In cases in which the systolic pressure was elevated two basic types of response were described: (A) that in which the systolic pressure failed to return to the preinjection level within the 25-minute period, and (B) that which showed a return to the control level during the observation period. Those subjects showing the first type of response were considered, by the authors, to have a significantly more favorable prognosis when subjected to EST than those showing the second type of response. The underlying physiological mechanism explaining these results was attributed to excess epinephrine-like secretion in the (A) type, while the (B) type was said to have an excess of arterenol-like secretion (Fig. 1). This explanation was based in part on the hemodynamic measurements obtained when normal subjects were given methacholine during the infusions of epinephrine and arterenol (norepinephrine).[2]

The present study is concerned with the measurement of the excretion of epinephrine (E) and arterenol (NE) before and during the methacholine test and the relation of these findings to the hemodynamics observed in normal and schizophrenic subjects.

Method

Ten normal subjects, eleven chronic schizophrenics, and four acute schizophrenics were given the methacholine test.[3] The subjects arrived for the experiment at 9 a. m. and for the control period remained in bed for one hour, at the end of which a urine sample was collected. The methacholine test was then begun, with the usual five-minute period in which blood pressures and pulse rates were taken every minute. Saline was then injected intramuscularly, and every minute for the next 10 minutes blood pressures and pulse rates were recorded. At this point 10 mg. of methacholine chloride was administered. Pulse rates and blood pressures were recorded every 30 seconds for the next 2 minutes and every minute for the following 23 minutes. At the end of the experiment, a second urine sample was collected which was thus the methacholine-test sample, as compared with the first urine collection, which was the control sample.

A selected number of chronic schizophrenic subjects were infused with epinephrine or arterenol and were given the methacholine test during the infusion.

Urine samples were hydrolyzed by boiling for five minutes after acidifying and extracted by the aluminum oxide (alumina) adsorption method described by von Euler and Hellner.[5] The extracts were then bioassayed by a modification of the technique described by Gaddum and Lembeck.[4] This method consists of testing the sample on the

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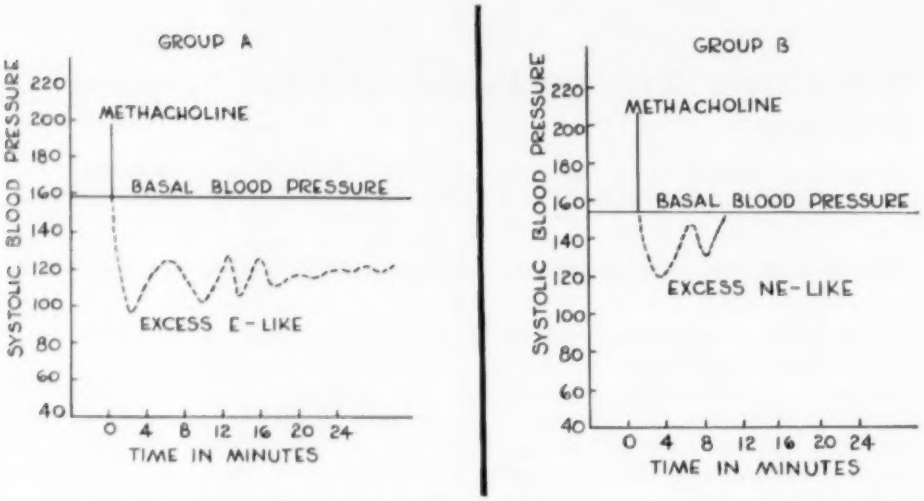


Fig. 1.—A and B type reactions to methacholine test. Area is that portion of the graph from the initial fall in the systolic pressure after methacholine administration to the point of its return to the control level.

rat colon for arterenol and on the rat uterus for epinephrine. The bioassay is based on the quantitative inhibition by the amines of the contraction induced by acetylcholine in vitro in a 2 cc. bath. The rat colon is approximately equally sensitive to the two amines, whereas the uterus is 75 to 300 times as sensitive to epinephrine as to arterenol.

Results

Relation of Resting Systolic Pressure to Arterenol Excretion.—Figure 2 shows the relationship of the resting systolic blood pressure to the arterenol excretion. The normal subjects show a positive correlation between systolic pressure and arterenol excretion of 0.74, which is significant at better than the 1% level (Table 1). When all three groups of subjects are included in the statistic, there is an r value of 0.55, which, though lower, is still significant at better than the 1% level of confidence. In the upper left-hand corner of Figure 2 we observe two chronic schizophrenics who show relatively high systolic pressures and display very low arterenol excretion. These two subjects were tested in two additional experiments and were found to show a consistently high systolic pressure with low epinephrine and arterenol excretion rates. These two subjects were not included in the statistic. Both these subjects showed elevated pulse rates of 80-90 per minute in

Fig. 2.—Relation of the mean resting systolic pressure to arterenol excretion rate during the control period.

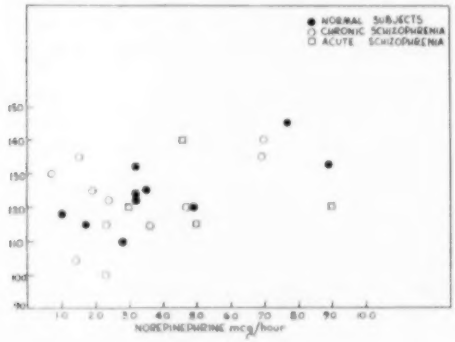


TABLE 1.—*Relation of Resting Blood Pressure to Arterenol Excretion*

	N	r	P
Normals	10	0.74	<0.01
All subjects*	23	0.55	<0.01

* Two chronic schizophrenics, who gave on repeated testing a high systolic pressure with low epinephrine and arterenol excretion values, were omitted.

TABLE 2.—*"Area" and Excretion of Epinephrine and Arterenol Excretion in Normal and Chronic Schizophrenic Subjects*

	Before Methacholine, γ/Hr.		After Methacholine, γ/Hr.		
	Arterenol	Epineph.	Arterenol	Epineph.	"Area", Units
Normals (10)	4.0±0.63	0.33±0.10	4.9±0.66	0.41±0.12	9.0±1.4
Chronic schizophrenics (11)	3.2±0.60	0.66±0.28	3.2±1.0	0.23±0.05	44.0±9.0 $P<0.01$

each instance. It is also worthy of note that the acute schizophrenics, though few in number, do show marked individual variations. However, in general, it is evident that systolic blood pressure proves to be correlated with arterenol excretion, with the correlation highest in normal subjects.

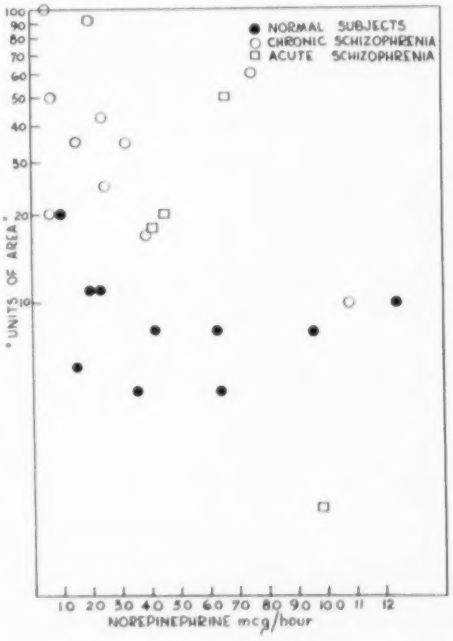
Relation of Area to Epinephrine and Arterenol Excretion.—That aspect of the methacholine test which proved to correlate best with excretion data was area (Fig. 1). Area included that portion of the test from the point of fall in the systolic blood pressure with the administration of the methacholine to the point of its return to the control level, which may be considered the time of reestablishment of homeostasis. No significant differences were observed between the pre- and postmethacholine excretion rates of epinephrine or arterenol (Table 2). Furthermore, because of the great variability of excretion levels, no generalizations could be made which applied to controls as contrasted with patients. However, the area computed for chronic schizophrenic patients was significantly greater than observed in controls (Table 2). When the log of the area of all subjects studied was correlated with the excretion of arterenol during the methacholine test, there was a correlation coefficient of −0.51, which was significant at the 1% level (Table 3). Since there was a significantly greater area observed for the chronic schizophrenics over that for the controls, graphically the points for the patients were deployed quite separately from those for the control subjects (Fig. 3). Thus, for the same levels of arterenol excretion, the chronic schizophrenic patients showed a

TABLE 3.—*Relation of "Area" to Epinephrine and Arterenol Excretion*

All subjects	N	r	P	
Arterenol *vs.* log of "area"	25	−0.51	0.01	
Epinephrine *vs.* log of "area"	25	−0.05	NS	
All schizophrenics				
Arterenol *vs.* log of "area"	15	−0.51	0.05	
Epinephrine *vs.* log of "area"	13*	0.63	<0.05	>0.01

* One chronic schizophrenic, who had the lowest arterenol excretion, and one acute schizophrenic, who had the highest arterenol excretion value, were omitted from the statistic.

Fig. 3.—Relation of area to arterenol excretion during the methacholine test period. Unit of area equivalent to 0.25 sq. cm. on graph: No. 340 M Dietzgen Graph Paper.

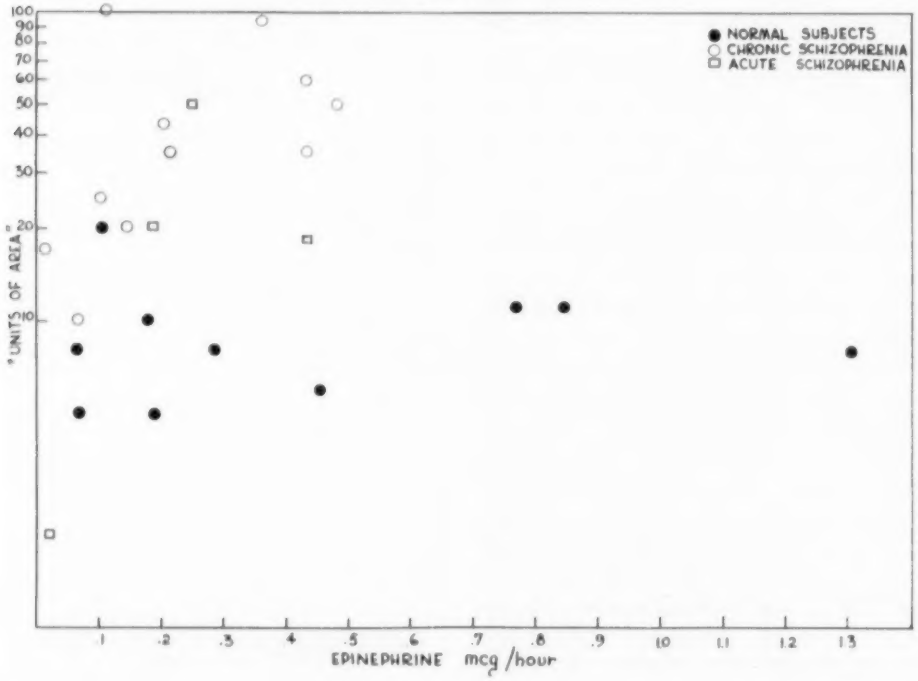


greater area in the methacholine test than the controls.

The correlation coefficient of the log of area of all subjects studied with epinephrine excretion was −0.05. When the points were graphically plotted, a sharp separation of the schizophrenic subjects from the controls was noted (Fig. 4). Where the controls showed no relationship of the log of the area to the epinephrine excretion, the schizophrenic subjects showed a positive relationship, with an r of 0.63, which was significant at better than the 5% level but not at 1% (Table 3). It is highly probable from these results that the epinephrine secretion contributes in part to the greater area observed in the schizophrenic subjects.

Methacholine Test During Infusion of Epinephrine or Arterenol.—After the infusion of epinephrine, both adrenalectomized[5] and adrenal-intact subjects[6] show only 0.5%-1.0% of the infused amine in the urine above that of the preinfusion control. On the other hand, when arterenol is infused, 3%-6% of the amine is recovered in the urine. When graded doses of epinephrine were given to the same subject on different days at the doses of 0.05γ, 0.10γ, and 0.20γ per kilogram per minute for 30 minutes, increasing amounts of the infused amine appeared in the urine with no consistent change in arterenol excretion.[6] Similarly, when arterenol was infused in identical manner, increasing amounts of the infused amine appeared in the urine without consistent changes in epinephrine excretion. As might be expected, the hemodynamics in these experiments indicate that with increased epinephrine dosage there was an increase in the systolic blood pressure and a decrease in the diastolic pressure accompanied by tachycardia, whereas in the case of the arterenol infusion there was an increase in both the systolic and the diastolic blood pressure accompanied by bradycardia. The relation of arterenol excretion to dose

Fig. 4.—Relation of epinephrine excretion to area.



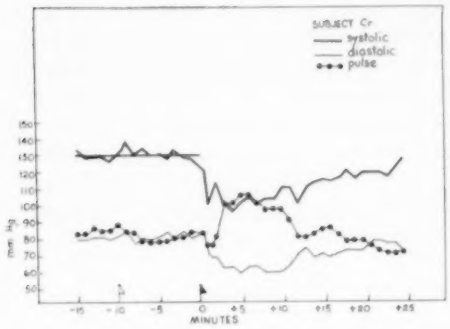
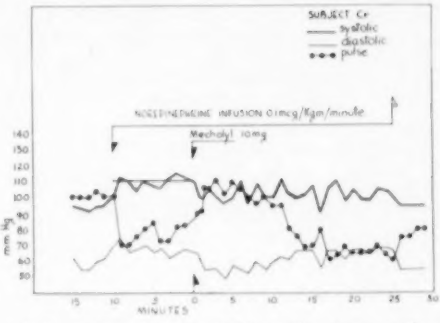


Fig. 5.—*A*, hemodynamics of Subject Cr during regular methacholine test. Excretion of arterenol during the test period was 2.0γ/hr. and that for epinephrine 0.36γ/hr. Area was 93 units.



B, hemodynamics of Subject Cr given methacholine test during arterenol infusion (0.1γ/kg/min.). Excretion of arterenol during the test period was 3.4γ/hr. and that of epinephrine 1.11γ/hr. Area was 90 units.

level was linear.[7] There was a doubling of the excretion of epinephrine with the doubling of the dose of epinephrine from 0.05γ to 0.10γ per kilogram per minute; however, with the subsequent doubling of the dose from 0.10γ to 0.20γ per kilogram per minute there was a sevenfold increase in the excretion of epinephrine.

A selected number of chronic schizophrenics were infused with epinephrine or arterenol at a dose of 0.1γ per kilogram per minute, and methacholine was administered during the infusion. Figure 5 depicts a subject with large area which was decreased with arterenol infusion, while Figure 6 shows a subject who was infused with epinephrine and the area increased.

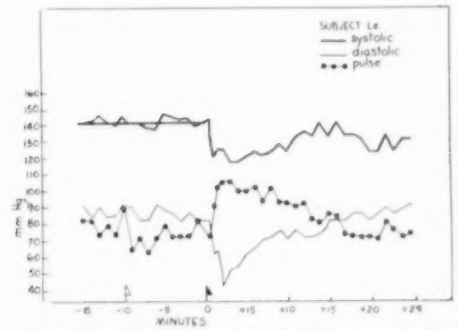
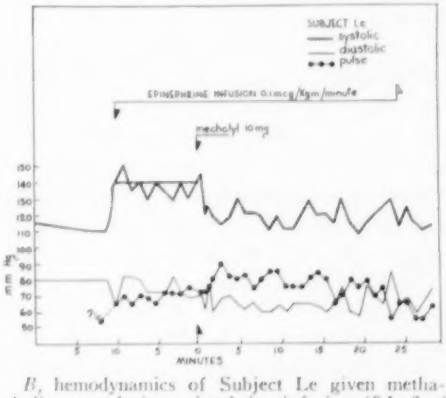


Fig. 6.—*A*, hemodynamics of Subject Le during regular methacholine test. Excretion of arterenol during the test period was 7.5γ/hr. and that of epinephrine 0.43γ/hr. Area was 60 units.

Comment

These experiments confirm in part the explanation of the physiological mechanism given by Funkenstein, Greenblatt, and Solomon[2] for the methacholine test, namely, that the smaller area is related to arterenol-like secretion and the larger area is related to excess epinephrine-like secretion. These experiments permit, however, the following extensions and modifications:

1. The resting systolic blood pressure is related to arterenol secretion, not to epinephrine secretion. High blood pressures may be encountered in chronic schizophrenia when there is no indication from the excre-



B, hemodynamics of Subject Le given methacholine test during epinephrine infusion (0.1γ/kg/min.). Excretion of arterenol during the test period was 11.5γ/hr. and that of epinephrine 0.10γ/hr. Area was 28 units.

tion data that the elevated pressures are due either to increased epinephrine or to arterenol secretion. The latter group have another feature in common: an elevated pulse rate.

2. There is a negative correlation between the area and the arterenol excretion during the methacholine test. However, for the same levels of arterenol excretion, the chronic schizophrenic subjects show a significantly greater area than do normal controls.

3. In the statistic which includes all the subjects studied, there is no relationship between the log of the area and the excretion of epinephrine. However, the schizophrenic subjects show a positive correlation of log of the area to epinephrine excretion, while the normal controls show no relationship. This assertion must be qualified by stating that this is true for the levels of excretion observed in this study.

4. Infusion of epinephrine and arterenol at the rate of 0.10γ per kilogram per minute during the methacholine test confirmed in the schizophrenic patients studied that area was reduced with arterenol and increased with epinephrine.

Gellhorn, Nakao, and Redgate[8] reported that with the raising of the excitability of the posterior hypothalamus by pharmacologic agents (e. g., strychnine and pentylenetetrazol (Metrazol) or by subthreshold electrical stimulation in the cat, a reduction in the drop in blood pressure after methacholine could be effected. Furthermore, when lesions were placed in the same areas of the hypothalamus or when thiopental (thiopentone) was instilled, there was effected an exaggerated drop in blood pressure after methacholine. These experiments indicate that, with the hypotension induced by methacholine, one can evaluate posterior hypothalamic excitability. If one considers the results obtained in this sampling of chronic schizophrenic patients with respect to area after the methacholine test, a tenable conclusion is that there is a significantly lower posterior hypothalamic excitability in these subjects. Since epinephrine had a positive relation to area in the schizophrenic subjects but not in the normal controls, it appears that the concentrations of epinephrine observed in these experiments (or an unknown metabolite of epinephrine) apparently depress in some manner posterior hypothalamic excitability in the psychotics but not in the normals.

Summary

Normal and schizophrenic subjects were studied with respect to the relation of excretion of epinephrine (E) and arterenol (NE) to the hemodynamics of the methacholine test.

There was observed a positive correlation between the resting blood pressure and the excretion of arterenol.

With respect to area observed in methacholine test, there was a significant relationship (negative) with arterenol excretion, but with chronic schizophrenic patients showing a greater area than normal controls.

Epinephrine excretion was positively related to area in chronic schizophrenic patients, with no relationship evident in normal controls.

The central sympathetic representation controlling the secretion of epinephrine and arterenol is discussed, the inference being drawn that epinephrine, or a metabolite of epinephrine, is implicated in some manner to the depression of the excitability of the posterior hypothalamus in schizophrenia.

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The Use of an Anxiety-Producing Interview and Its Meaning to the Subject

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I

Our theoretical concepts of anxiety and their possible applications to the study of psychosomatic problems have been reported previously.[1] In a preliminary sketch of an experimental design, we indicated our purpose to evoke or augment free-floating anxiety in human subjects who were anxiety-prone to some degree, in order to determine the level, trend, and change in anxiety and simultaneous changes in several other psychological and somatic variables. In other words, we wanted to alter the emotional equilibrium in order to evoke and measure concomitant changes in other somatic and psychological functions.

This communication presents the methods used to stimulate anxiety through verbal and nonverbal communications in transactions between subject and psychiatrist in a particular setting, and to demonstrate the wide variety of possible meanings to the subject and the complicated effects that result from such a stimulation.

It was planned to produce graded increments in the level of anxiety by the use of appropriate verbal and attitudinal stimuli during successive daily psychiatric interviews, with an anxiety-prone subject selected from the inpatient population of this Institute. The psychiatrist had previous knowledge of the patient's illness, his life story, and a number of episodes in which free anxiety had been experienced in the past. After a preexperimental day intended to acclimatize the patient to the laboratory, we proposed to stimulate anxiety in a series of three successive days of experimentation. The position of the stress interview within the time span of the experimental days and its relation to other procedures of the study may be visualized in the accompanying Table.

In order to appreciate the complexity of the stress interview, other factors in the setting should be known. Capable of influencing the stressor's attitudes and functions were other persons whose roles in the total situation were important. Among these were two psychiatric colleagues, acting as observers behind a one-way mirror, watching every move and listening carefully. Each subject-patient had his personal therapist, who was interested in the procedure for many reasons and either joined the observers behind the one-way mirror or questioned his patient in a later therapeutic session regarding the effects of the experimental procedure. Naturally, the therapist did not want his patient unduly upset, nor did he approve of interference with his therapy. However, soon it became clear that the experimental procedures, particularly the stress interview, elicited information which was helpful to the therapist. Often the stressor arranged for a consultation with the therapist to communicate this information, so that soon an implicit demand on the stressor to "give" something of value to the therapist became a common occurrence.

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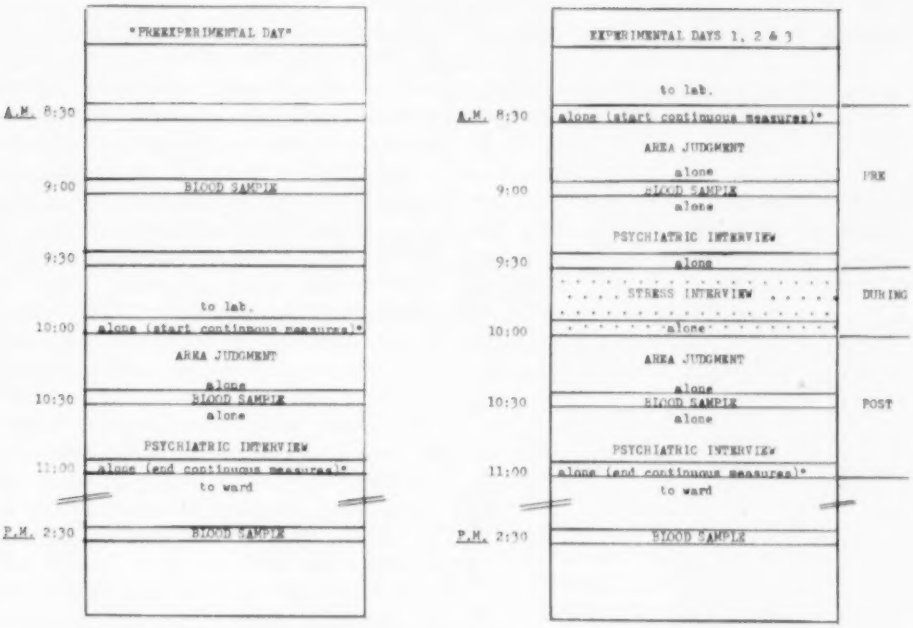
EXPERIMENTAL SCHEDULE



*Heart and respiratory rate, body movements, observation through one-way screen recorded continuously during period in laboratory.

This took the form of added knowledge of psychodynamics or diagnosis, and often suggestions for a fruitful therapeutic focus.

Members of the research group who were responsible for measuring changes in other variables were concerned with the stress interview in the hope that sufficient free anxiety could be evoked and reflected in significant changes in their own systems. Also the entire professional hospital personnel, composed of residents, nurses, attendants, etc., knew about the research and were curious about what was being done. They needed to know the purposes of the experiment, what was done, and the anticipated effects in order to understand their roles in keeping the patient in the experiment during the entire period, and to deal adequately with the patient's responses on the nursing unit after each day's procedure.

Although there were many interested people in the background, only the two psychiatric observers advised the stressor as to what qualities of affective processes, defenses, and behavioral manifestations had been released during or after the stress interview. Often valuable suggestions as to changes in tactics were transmitted to the stressor for use on the subsequent experimental days.

The explicit role chosen by the stressor as a means of evoking emotional change was based on a knowledge of the subject's personality derived from a detailed psychiatric history and anamnesis. The interview was transactional rather than set in a pattern uniform for all subjects. Questions were asked or statements made, and the subject's responses were considered as informational feed-back, to which the stressor responded, when indicated, with shifts in direction or intensity of further questions or statements. The stressor's general attiture was one of permitting or urging anxiety. Although the patients often attempted to convert the interview into an anxiety-

allaying procedure, the stressor usually tried to avoid any attempts to decrease anxiety. Sometimes, in order to maintain a level of achieved anxiety, he would abruptly leave the room without answering the pleading requests of the subject for reassurance.

At other times a patient's lack of emotional responsiveness to the stress gave little feed-back of emotional arousal to the stressor. This might have been due to depth and effectiveness of defenses, to unwise choice of significant cues, or to delay in appearance of anxiety within the short period of stimulation. The stressor then developed a sense of ineffectiveness and frustration, leading to more persistent and aggressive attempts to evoke anxiety.

To evoke emotional responses, the stressor utilized a variety of tactics, which can be classified into three categories: (1) a discussion of the subject's severest psychological conflict; (2) an assumption of a specific attitude toward the subject, and (3) a disturbance in communications with the subject. The initial attempt was usually focused on the subject's severest psychological conflict. For example, a man might be confronted with the fact that his love and worship of his father were in conflict with a coexisting hostility toward him. Sometimes the stressor focused on the subject's defenses, such as in the case of the compulsive handwasher, who was told that this was a defense against a wish to be dirty. The stressor often acted a posed role in an effort to disturb the patient. He would behave as if *he* were anxious and restless, or he would act cold or harsh or seductively tender. In appropriate situations the stressor would refuse to respond to the subject's role assignments and behave in a rejecting, noncomplementary manner. Another tactic consisted in blocking or impeding communication by not understanding or by misunderstanding the subject's words or meaning, and one patient's name was deliberately and repeatedly mispronounced. Once the subject's phobic object—a dog—was brought into the experimental room, and another time disorder and messiness were created in the case of a compulsively clean subject. When these or other variations in the stressor's behavior or attitude were not intentional, the concealed observers were able to detect and record them.

Balanced against the stressor's intention of increasing the subjects' anxiety by disturbing their psychological equilibrium in the interview transaction were implicit attitudes which often interfered with the achievement of his purpose. In his role as a clinical psychiatrist much of his life had been devoted to treating patients. When anxiety was evoked with deliberate intent, the patient's suffering and pleading for reassurance automatically stimulated his implicit therapeutic role. As a result, he consciously and unconsciously set limits to his stress interview. When the patient's anxiety increased to the degree that threatened to disrupt his cooperation in the experiment, the stressor not only decreased his stimulation but often neutralized it with verbal or nonverbal reassurance. These implicit attitudes were reinforced by his knowledge that psychiatric colleagues acting as observers, or otherwise apprised of his role as a stressor, were aware of what he was doing. Thus the "ghosts" behind his back acted as restraints.

Prior to the experiment each subject was fully informed that the procedures employed were designed for our research but that the results would probably be helpful to his therapy. The patient was usually cooperative and helpful. After he had recovered from the anxiety of the preexperimental day, during which he adjusted to a strange room, mysterious apparatus, and new people, the subject usually was well motivated to cooperate in the experiment. He wanted the testing to reveal more about his problems to himself, and his therapist and he desired to be helpful in the research program of the Institute. He was committed to the experiment at first with varying degrees of self-interest and altruism.

His implicit attitude was, however, entirely concentrated on the wish to be helped. The experiment was conducted within the therapeutic milieu of a hospital in which all personnel are psychodynamically oriented, where psychotherapy is the dominant curative process and favorable results are the rule. In spite of explanations that the procedure was experimental and for the purpose of eliciting information, the patients often assumed that it really was a therapeutic process. The stressor was usually the director of the hospital, which implied that the patient was specially chosen for unusual therapeutic attention. Implicitly interpreting that the stress interview was helpful and therapeutic tended to neutralize the effectiveness of its anxiety-provocative intent.

In the transactions between subject and stressor, information was continually being fed back from one to another. Since the goal of the stressor was to induce a change in emotional level, he persevered when he observed or received information from the subject that anxiety was being intensified but stopped short of evoking severe restlessness or an intensity of anxiety which he believed would endanger the subject. When the stressor received repetitive information indicating that no emotional change or no further increment of affect was likely, he terminated the interview.

The results of the interview on any one day determined the tactics of the stressor on the following day. However, his contact with the subject was brief, and the fragment of behavior available for his information was largely verbal and exclusively in a two-person situation. The psychiatrists behind the one-way mirror observed the subject before, during, and after the interview designed to evoke a stress response and thus had a longer time span for their observations, including several periods when the patient was alone and could behave with fewer restrictions. In addition, they conducted evaluative interviews (Table) to assess the subject's state before and after the stress interview. The observers assisted the stressor in deciding what changes in intensity, content, or role patterns to make without disclosing to him their affective ratings.

After each of the three experimental days the stressor made an independent estimate of the strength of his stimulation in terms of its presumed efficacy in changing the level of anxiety. The stressor attempted to rate what he did, or thought he did, in attempting to arouse an anxiety response and not the response itself; in other words, the stimulus and not its effects. He considered that he was much too busy in the transaction with the subject to qualify or quantify the subject's responses during this brief period. His ratings were almost entirely subjective, derived from his sense of intended intensity strength; yet they were inevitably influenced by the information fed back through the subject's responses.

II

The following brief vignettes of 8 of our 19 subjects illustrate the wide range of techniques employed by the stressor in his attempts to alter the patient's affective state. They also illustrate the variety of mechanisms utilized by patients with differing characteristic mechanisms of defense to cope with the potential stress. In effect, the stimulus interview became a rapidly changing field in which the interviewer constantly utilized feed-back from the patient to determine whether he should become more reassuring or more stressing. At times, the signals could not be adequately interpreted and numerous "paradoxical" responses occurred.

CASE 1.—This 38-year-old man complained of multiple phobias, fear of open streets, heart disease, and a morbid fear of death, associated with intense free-floating anxiety. The latter was observed objectively in generalized tremors, muscular twitchings, and intense restlessness. As he described these sensations, "I am scared something is going to happen to me. I feel shaky as hell inside." The patient was originally admitted to the hospital several years before, and, after treatment had allayed his anxiety, he was managed as an outpatient. After the present remission, the

patient entered the hospital, for the second time, complaining of extreme anxiety with a feeling of impending death. His present attack began when he was ridiculed by his wife for wanting to buy a power-tool. Despite this, he bought the tool and then found that he was unable to cross the street without pain in his chest, difficulty in breathing, and a profound attack of anxiety.

On the first experimental day he was less agitated and lacrimose than on the preexperimental day but still described tension in his head and nervousness in his stomach. Tremulous movements developed after the first blood drawing. The stressor probed the reaction of the patient to his mother's death, which had occurred six weeks prior to hospitalization, and emphasized the possibility that the fear of having a heart attack or a stroke and dying could be realistic. Essentially he communicated to the patient, "What is so bad if you do have a heart attack?" He also ridiculed the patient's weekend attacks of anxiety by asking, "Why don't you carry your doctor on your back all the time?" As he left the room, the psychiatrist took with him the patient's magazine, which the latter had assiduously read to defend himself from anxiety when alone. The patient was agitated and restless in the period immediately after the interview, but later he told the evaluative interviewer that he was confused, but impressed with the stressor's frankness and calm and honored by the interview. The patient minimized the importance of the interpretations of his reactions to his mother's death and interpreted the interview as "adverse psychology" which should have a positive benefit for him. In general, the first day was mildly reassuring.

On the second day the subject showed only minimal evidence of agitation and described himself as relaxed and able to go home. He felt less anxious than he had been for some time. The stressor behaved quite differently than on the previous day because of the absence of a prolonged stress response. He was restless, paced the floor, rearranged the furniture, and expressed frequent misunderstandings of the patient's communications and accused him of lying. He asked, "Where has your anxiety gone?" He was the opposite of calm and reassuring because he acted as if the patient made him nervous and dissatisfied. After the interview the subject had a troubled expression. He was restless and somewhat tremulous and indicated that he was all upset. He interpreted the psychiatrist's attitude as an attempt to stir him up and make him angry. He was anxious immediately after the stressor left the room and described a peculiar tightening sensation in his head and stomach throughout most of the subsequent experimental period.

On the third day the subject was not so comfortable as he had been initially on the second day, for he anticipated trouble with the psychiatrist and tried to structure the interview as a friendly session with him. The stressor, however, pursued the patient's relationship with his father and interpreted his dependency and hostility toward him, the subject rejecting this vigorously. Then he discussed the patient's fear of death and persisted in interpreting the patient's own death wishes toward his father. The patient contrasted the psychiatrist's behavior with that of the day before and attempted to defend himself against his increased anxiety by concentrating on a magazine. He had, nevertheless, two acute periods of anxiety—one when a technician entered the room for a blood sample, and another when a match was inadvertently lit in the observation room and the patient saw it as if it were above his head and thought that he had set his hair on fire.

This case highlights the complexity of the stress interviewer-subject relationship. On the first day certain implicit roles of the interviewer (helpful physician, skilled psychiatrist and director of the hospital) outweighed his current explicit role of stress inducer. The subject responded also to the personality of the interviewer, being especially impressed with his frank, calm manner. He utilized the first day's developments as a nucleus upon which to erect transitory defenses, and he anticipated behaving in a similar fashion on the second experimental day. The interviewer, upon receiving information from the psychiatric observers and integrating this with feedback received in his contact with the patient, decided to alter his manner and change his role. He no longer was the "understanding physician," nor was he the unperturbed logical observer. The shift was effective in evoking anxiety in this subject. Because the subject expected another "silly discussion," another shift was made on the third day to a serious, vigorous interpretation of hypothetical unconscious motivation. Although this was denied, it potentiated a later anxiety response to incidents in the laboratory.

A transaction had developed between patient and interviewer which necessitated the latter's understanding the rapidly changing

response of the subject in order to achieve a stress response. Without this understanding and change, as when a standard interview is utilized for every subject, the stimulus would have been ineffective as a stress.

CASE 2.—This 44-year-old male business manager had been hypertensive for 30 years, but for some time lately he had been diffusely anxious and about a week before admission a doctor had told him to take care of himself or some dire event would occur. After this, he developed insomnia and anxiety over impulses to kill his wife and child. The only alternative to going crazy was to kill himself.

The patient had been anxious most of his life, for he remembered anxiety while in school and playing sick in order to stay home. His anxiety, although fairly steady, had at least one sharp exacerbation when he was in a barber shop, where he developed a fear of dying in the street when the barber offered him a cigar. In the hospital the patient expressed much regressed symbolic verbalization, feeling guilty because of fellatio experiences. In occupational therapy, when making tulip earrings for his wife, he punned on the word "tulip" and became anxious over its implications. When doctors breathed deeply in his vicinity, he feared that they were passionate with homosexual feelings toward him.

Although the day prior to preliminary testing had been quite disturbing and the patient had been close to a panic, on the preexperimental day his anxiety, although still present, had diminished. On this day his peak anxiety developed during a test of perceptual discrimination, when he saw the procedure as a measure of mental deterioration. On the first stress day he started out somewhat more disturbed than previously, with anxiety about disintegration, and depression, which chiefly revolved around guilt over bad thoughts. The stressor utilized the information regarding the patient's latent homosexuality and spoke seriously about loss of control, as well as his fears of disintegration. The patient's attitude was that the psychiatrist was making strong interpretations in a fairly benign and matter-of-fact tone which should be helpful. However, the interpretation stirred him sexually, and he had bizarre associations of impregnation during the blood drawing. His weak denial was effective only for a short period of time, and later evaluative interviews revealed that the subject had accepted the stress interviewer's interpretations. There were, as a result, increased anxiety concerning the possibility of disintegration, with confusion, and also increased feeling of sexual excitement. Although there was objective evidence of disintegration, there was less evidence of subjective concern over it.

During the second day the patient attempted to prevent a repetition of the previous day's anxiety and focused on the present reality. The stressor attempted to concentrate on the anxiety over loss of control of destructive impulses. He also brought up the question of homosexuality again. The patient became violently angry and rose up, threatening to strike the psychiatrist. The interviewer firmly told him to sit down, and the patient obeyed. The massive rage and threat of violence was the immediate reaction to the persistence of interpretations, but the stressor firmly quieted this down and paranoid behavior and obsessive ruminations then appeared. Vigilance increased, and the patient sought aspects of danger and threat in the immediate environment. Anxiety and depression rose in the period after the stress interview, and the patient became quite disturbed. The peak anxiety occurred when the patient was alone, and he desperately tried to control this with suppressive devices. He became confused, however, and showed partial amnesia for the interview and could not concentrate on tests of perceptual discrimination which followed.

On the third day the stressor attempted to ascertain whether the patient had thought about the material covered during the previous day. The subject became angry and sarcastic and threatened to get nasty. He tried to turn the questions around, ignore the psychiatrist, and assume an air of nonchalance. He said: "Now you're starting again. I don't want my thoughts brought to me. I want to pull myself together." The rage persisted for the rest of the morning after the interview, with less confusion than on the previous day. Denial seemed to be adequate except that he broke down, sobbed, and became quite agitated for a few moments after the stress interview. He tried to pull himself together and apparently was successful at the time of the perceptual tests. By the last evaluative interview he was striving to be euphoric and made such sarcastic statements as, "I haven't felt as well in 40 years."

In this case the observational data indicated the delayed effect of the first stress interview. A relatively neutral stimulus, the blood sample, became extremely stressful in view of the lowered threshold to stress induced by the stimulus interview, residues of which were present throughout the next two experimental days. The dramatic occurrence on the second experimental day, when the patient's threats to the psychiatrist were responded to by a calm, firm attitude,

limited the explosive aspect of the patient's behavior and changed the course of the experiment. On all three experimental days the stressor's tactics were the same in spite of the subject's attempts to avoid discussion of his central conflict, even to the point of threats. On each day the technique consisted of a direct confrontation with unacceptable attitudes, and the result was considerable emotional turbulence.

CASE 3.—A 30-year-old housewife entered the hospital with a complaint of acute panic attacks for one month. Just prior to this, the patient had confessed for the first time to a group of female co-workers that she was unable to have children. The patient's husband had been engaged to her before going overseas during World War II. He stopped writing after he lost one testicle through a wartime injury. The patient kept writing and pleading with him to continue their relationship, and, actually, after the war they resumed their courtship and were married, and sexual relations were satisfactory. Then the husband lost his second testicle through a disease process and became impotent. As a result, the patient felt that she was unable to obtain satisfaction as a woman and, thus, was justified in being treated as a child, with all of her whims satisfied. She denied fantasies of other men and stated that she worried a great deal about her husband because he needed her so much.

The anxiety attacks were associated with palpitation, profuse sweating, and fear that she would "blow her top." The patient had had to leave work and, during her anxious episodes, often ran to her mother's house to weep. She finally confessed her sexual problems with her husband to her mother and obtained only temporary relief. She felt it was unworthy of her to think of other men or want to leave her husband.

In the preexperimental day she developed the hypothesis that she was observed through the one-way mirror and seemed to enjoy this possibility. She seemed to have a feeling of excitement centered in her lower abdomen, somewhat like a sexual feeling. The patient was concerned about the procedure but clearly indicated that she felt the tests were arranged for her own good and that the examiners knew what they were doing.

On the first experimental day the stress was focused on content spontaneously brought up by the subject. At the start of the interview the patient related to the psychiatrist as a therapist, telling him what was disturbing her. The stress focused on the interpretation that the patient must have some bad thoughts, which explained why she felt that people did not love her and that these bad thoughts had something to do with sexual feelings. The stressor urged her to look into the mirror and asked her what she saw there. Did she see a bad girl in the mirror, or did she see two different people in the mirror? The patient seemed very anxious at this point and asked the psychiatrist what he meant by this. He had implied that she was literally splitting in two, and disintegrative anxiety was evoked. The psychiatrist, however, relieved the patient a great deal by explaining that he wondered whether she saw both a good and a bad part of herself in the mirror. She spent a large part of the remaining period in the laboratory looking in the mirror and mastering the "bad part" of herself. She felt considerably better in the latter part of the morning. The psychiatrist, she thought, was trying to get something out of her, but his motive was "to help me and I am thankful that he questioned me in that way."

The patient felt much better initially on the second day, having been relieved by the previous day's interview. The stressor concentrated on her sexual feelings and wanted to know whether the patient wished to crawl into her mother's bed and take her mother's place with the father. There was an implicit threat that the patient would have trouble with her mother if she acted out sexual impulses with her father and that her mother would then disown her. He vigorously pursued these incestuous fantasies and all the defenses erected against them. The patient weakly tried to deny the implications of the statements about her sexual feelings and used confusion as a defense. To another psychiatrist in a subsequent interview the patient indicated that she had anger toward the stressor and the other testers and was depressed about the implications in the material. There was considerable anxiety about the possible loss of mother. She became increasingly disturbed during the day and had to be seen by the resident on duty. Still later in the day she developed the hypothesis that she must have homosexual feelings about her mother and that she really wanted her sexually, rather than the father.

The third day began with the patient's being quite anxious and wanting the door left open as each person left the room. She felt that she should not have come down this morning and had fantasies of the stressor coming through the window. The stressor, a different person than on the previous two days, deliberately tried to block communications with the patient and misunderstand her. The patient's voice became loud, and she tried desperately to make him understand. She was told that she was not cooperating and was shifting from one subject to another. The patient leaned forward as if attempting with body posture to

communicate with the psychiatrist, but his attitude blocked this and she became increasingly anxious, depressed, and irritated. She developed a hypothesis that the stressor was trying to confuse her and to get her angry and frightened. There was puzzlement as to who was crazy—"they or me?" The anxiety had a disintegrative quality in that it indicated that she might be going to pieces, as she said, "I was afraid that I was going batty." The stress on this day successfully increased the patient's anxiety.

During the first day the interviewer shifted from his explicit role of stress inducer to his role of therapist when he perceived too rapid development of anxiety. This converted an experimental day into an over-all reassuring one but also permitted the completion of testing in this subject. On the second experimental day the stressor used direct interpretations of fantasies close to consciousness which evoked considerable anxiety. Blocking of communication was utilized on the third day, and the response was quite intense.

CASE 4.—A 39-year-old male electric contractor entered the hospital with tenseness and nervousness, rapid heartbeat, and crying spells, which began five weeks earlier, when his father died of a cerebral vascular accident. However, the patient felt that his illness began six months prior, when his father first manifested cardiovascular symptoms. When visiting his sick father, he experienced tachycardia, a tight feeling in his chest, and an urgent desire to leave. He defended himself by working harder in business; but, because of increasing nervousness, he began to drink in the evenings, coming home worn out and immediately falling asleep. He had been closer to his father than any sibling. They were on such good terms that they never quarreled, and his favorite memory was sitting around in the evenings drinking beer alone with his father.

His siblings were in a more favored position with the mother, and, although he had many reproaches and resentments against them, he had never been able to express his anger directly. He took pride in his continual defense of the underdog, never picked on anyone, and never became angry. At the age of 12 there was a period of rather sudden change of personality, when he ceased being scrappy and getting into fights. He has always worked hard, and until recently his business had expanded.

On the preexperimental day the patient entered the testing situation after having recovered from his severest anxiety and depression, evidenced on admission to the hospital. However, he was concerned over the apparatus and had a feeling of uneasiness and anxiety at the start of the perceptual test. He also felt anxious when left alone in the room.

The focus of the stress on the first day was clearly one of content, pursuing the patient's need for his father and signifying that, although he was putting up a good front, he was like a scared little boy. He was urged to permit himself to feel anxiety and hence get to the bottom of his problem, with the implication that this would be therapeutic. The patient was told that he had an intense feeling of loss and a need to be close to his dead father. At first he defended himself against this interpretation, but the stressor indicated that this was an intellectual front. Soon the patient admitted anxiety with such statements as, "I don't know what I'm scared of, but I'm awfully scared." When urged to continue feeling his anxiety, he cried profusely and then stated he got a great deal of benefit from the crying. At the end of the interview, he said, "I'll never run away from my anxiety again." Later he described an immediate feeling of relief, especially after the psychiatrist left, characterized by warmth in his chest and easier breathing. He also said later that it was pleasurable to cry, and he described a "warm sadness" for the remainder of the morning.

The patient had apparently recovered a great deal by the second day and described his feelings of relief and relaxation. He greeted the stressor with, "You're the one that did it. You're the one that helped me get well." The focus of the stress on this day was on "possible additional areas of problems," especially the patient's anger at his father. This was brought out in the context of his feeling of desertion by the father's sickness and death. The psychiatrist told the patient that he felt like a little boy who was angry at his weak father's desertion. Again the patient attempted to defend himself by denial, but this was ignored, and soon the subject admitted that he did feel angry, and, at the end of the interview, he made a sudden decision to allow himself to blow off more steam. Again he thanked the stressor and said that, although his heart had been beating quite fast just before he entered the room, the possibility of talking to him again had been pleasurably anticipated. The patient tried to accept the suggestion that it was good to express anger, but there was anxiety in this new role. The anxiety seemed to be concerned over the possibility that his aggressive impulses might be too strong. This day was relieving, but not quite so much as the previous day.

The third day started off differently from the other days, for the patient told of being angry at the hospital and being angry during the perceptual test. He felt under observation during the test and indicated that he needed no more help.

The stressor focused on areas that had not been discussed previously. There was much silence during this interview, the patient looking disturbed. Whenever communication occurred, there seemed to be a drop in anxiety. He did not accept the fact that there were any loose ends that needed discussion and essentially repeated the insights that he had gained on the first two days. By the late morning his anger had receded and his self-esteem increased. He said, "I feel a new equality with the people who tested me." From the entire procedure the patient had a therapeutic result and was able to leave the hospital a few days after the end of the testing.

This case was characterized by a marked therapeutic effect in which the interviewer's exhortation to the subject to become anxious was successful but in a manner which signified mastery over a poorly repressed conflict. This subject developed a strongly positive relationship to the interviewer and responded quite positively to most of the procedure. Although he developed increased anxiety on the first experimental day, he experienced relief in the long-range sense as his hope of mastery increased.

Case 5.—The patient was a 36-year-old married waitress who entered the hospital after a year of fear of losing her mind. She was a thin, tense person who appeared younger than her age and constantly asked for reassurance about possible insanity.

Her present illness started while she was working at an Army headquarters as a waitress. She became nervous and tense when a new officer took charge and began to assert his authority. Treatment with hormones and sedatives was not effective. She remained home for a month with palpitations, tremulousness, abdominal distress, and occipital headaches. A short time before admission she moved to a housing project, where she became jealous and suspicious of her husband and actually accused a neighbor and her husband of having sexual relationships. She attempted to return to work as a waitress but was overcome by anxiety and had to go home. She felt the urge to strike out against her husband without provocation.

On the preexperimental day the patient showed definite feelings of dread throughout the whole period of testing, which increased markedly when she was left alone with the doors closed. She developed tachycardia and extreme sweating and almost fainted during the perceptual test. The patient requested to get out of the chair on several occasions.

The subject seemed to recover on the first experimental day from the reaction of the preceding day and seemed more oriented to the experimental tasks. The stress was focused on the patient's fear of disintegration. When she spoke of insanity in a friend, the stressor asked if she thought insanity was contagious. He also discussed jealousy and implied that it was one of the first signs of insanity. The tone of the stressor was accusatory and nonsupportive throughout the interview. The patient attempted to defend herself but seemed unsuccessful and described severe palpitations. The psychiatrist was persistent in asking her to imagine how she would act if she became insane. She talked of losing control and throwing things, perspired a great deal, and seemed agitated. She tried to defend herself by saying, "I just want to get well." When she asked if she would get over her nervousness, the answer was a noncommittal "I don't know," and his last words on leaving were, "This is all very serious." The patient's response was that of increased respiration and perspiration. The furrows on her brow deepened, and she showed quite a serious reaction. She cried occasionally and finally slumped down in her chair and fell asleep. She woke up rather agitatedly just before the perceptual test and was relieved to see the testers.

The stress seemed to be effective in attacking several levels of defense. It threatened her basic integrity and normality. It implied that jealousy leads to insanity, and it evoked guilt and shame in addition to disintegrative anxiety. The superstructure of defenses erected between the preexperimental day and the first experimental day was not capable of handling the interview. In the afternoon after the first stimulus interview the patient continued to be anxious, and her doctor responded to her anxiety by requesting that she cease participation in the procedure. The observers felt, however, that she could have continued.

The stress was focused on weakening the subject's defenses against loss of control and disintegration. It resulted in release of anxiety too great for the patient's or her therapist's tolerance, and correspondingly her blood corticoids rose to 63γ per 100 cc., the highest level due to a stress stimulus in this series of subjects. Thus she was taken out of the experiment, but the experience was helpful because the patient soon re-

established her equilibrium, recovered socially, and returned to work.

CASE 6.—A 26-year-old divorced woman entered the hospital in an extremely frightened state. She had many doubts about staying because of inability to face strange people and strange situations. The patient was in constant terror of coming in contact with dirt and, therefore, was afraid to touch anything or anyone, afraid to use the toilet, and doubted the cleanliness of her room, linens, towels, etc. She had frequent compulsive handwashing, so that her hands were swollen, red, chapped, and cracked.

Her illness started seven years earlier, when her first husband was killed accidentally in the service. Her handwashing ritual and phobia of dirt and germs began at that time and never left, although they had waxed and waned. The patient remarried and had considerable difficulty with her second husband, finally divorcing him. She had been in several sanitariums and received electric shock treatment. The patient tried to settle down in another state but became an alcoholic and sexually promiscuous. She now had returned to her mother's home, where the obsessive-compulsive symptoms had become progressively worse.

On the preexperimental day she was anxious and angry and complained strongly about the perceptual test. She was markedly obstinate and developed a procrastinating recalcitrance, which indicated a struggle over her responses. Several times she expressed a concern that the testers would think that she was worse than she actually was. She feared all of the apparatus because of the possibility of contamination.

There was some recovery from the previous day's disturbance on the first experimental day, but she still had much anxiety about the perceptual test because of the possibility that it might reveal her disintegration. The stressor pushed quite hard into the problem of cleanliness, indicating that the patient really wanted to be dirty. She was visibly angry and tried to deny this and accused the stressor of not understanding. He pushed harder and talked about her desire to throw mud, soil her pants, and have dirty thoughts. She became increasingly angry, anxious, and perplexed. At one point a dirty smudge was indicated on her forehead, whereupon the patient became anxious and the stressor left the room abruptly. The result was much disturbance to the patient, with increasing self-disgust and depression. Later she told the interviewer that she was angry at him for jumping to conclusions.

At the beginning of the second day there was apparent considerable recovery and composure. She seemed more depressed and less angry. The stress this day seemed to be more therapeutic in tone, although severer in content. The stressor pursued the patient's fear of insanity and exposure. He talked of her first marriage and the possibility that she was pleased to get rid of her first husband, also, that she had not got along with her second husband either. The patient seemed to develop less anger, but more depression and anxiety, looking very sad. She felt that the stressor was still jumping to conclusions.

The subject regretted that she could not present a better picture and was apologetic and disgusted with herself. Because it seemed apparent that the patient was developing a psychotic breakdown, she was not allowed to take the testing on the third day.

This subject was tested during a period of disintegration of compulsive defenses, which finally resulted in psychotic symptoms of a catatonic variety. The stimulus interviews were vigorous and may have played a part in the rapid loosening of defenses. She was one of three subjects who could not complete the experimental procedure because of the severity of their symptoms. Her mean blood corticoid level was the second highest of this series, reaching an extreme of 42.3γ per 100 cc. in the period immediately following the stressful interview on the second day.

CASE 7.—The patient was a 20-year-old single female college graduate, who had been acutely anxious and depressed for five days. The precipitating circumstances were the increasing pressure and backlog of work as a secretary. On the day of onset of her symptoms, she had been criticized for not doing her work properly and felt hurt and misunderstood. She then did not feel capable of doing a good job and stayed away from work before entering the hospital. The patient had tried to please her employers but felt that she was not successful. She was told that she did not have the poise and maturity to be a competent secretary. This dovetailed with her own doubts as to her acceptability and capability and her need to please people and be liked by them. She had never been able to express anger, even when unfairly criticized. In the hospital she seemed to need a great deal of reassurance and clung to people around her. When her feelings were hurt, she was often close to tears but at other times tried to whistle her troubles away. She used the techniques of working excessively, playing the clown, or creating an air of forced gaiety, when actually she felt like a country girl out of place in a high-pressure job in the big city.

She entered the test situation on the first day with low ratings for all affects, having become relatively comfortable and relating to people in a friendly way during her stay in the hospital. The

stressor used the method of responding in tangenital ways and not understanding the patient's communications, constantly trying to get her to clarify or modify her statements. For example, he deliberately called her by the wrong name and could not understand why the chart was in error. There was also some implied depreciation in regard to her ambitions, and the stressor was unresponsive to her varied, and sometimes urgent, efforts to get along with him. She was near tears at the end of this interview and, after the interview, cried with a good deal of irritation, impatience, and open anger.

On the second day she had recovered considerably, and the stress was similar to the previous day. The tangential communications were prominent, but less so than on the first day. The stressor included content in that her ambitions were depreciated, and he blocked her ingratiating efforts toward him by interpreting them. After this experience she was quite disturbed, and anxiety and depression were increased.

On the third day she was very angry from the start of the procedure. During the stress, roles were reversed, the stressor being reassuring and the patient repeatedly self-depreciating. She did not seem able to accept the reasurrance and seemed to be disturbed by the interview in spite of later efforts to ease her suffering.

This subject's first experimental interview was an extremely effective blockage of communication by means of a series of purposely misunderstanding comments. This served to evoke a response of depression and anxiety. On the last experimental day the interviewer shifted roles and attempted to be reassuring, but by this time the patient was self-depreciatory and could not accept such assurance. This case stands out because of the reversal of the explicit roles of the interviewer from "stress inducer" to "reassuring therapist." Both roles, however, were anxiety-producing because of changes within the patient as the experiment progressed.

Case 8.—This patient was a 49-year-old male attorney who had been a transvestite since the age of 5 years, at the time of his younger brother's birth. He had been in a hospital two years before because of a depression with phobias. At that time he was treated with insulin and electric shock and was discharged as slightly improved. His depression had begun when he was told that his dizziness and palpitation were not organic in origin. After discharge from the hospital, he improved somewhat, but, because of depression and obsessive thoughts of suicide, he began analytic treatment.

This therapy resulted in a decrease in his defenses and the development of obsessive thoughts of catching rabies and of developing tetanus from dog bites. Both the sources of his fears and the fears themselves gradually spread. The anxiety led to a severe palpitation, which, in turn, made him fear heart disease, and he had numerous physical examinations to check up on his somatic conditions. He developed a feeling of conflict between his "masculine and feminine parts," and his female fantasies increased in intensity. He was constantly angry with his family, becoming irritable and abusive to them. More recently he had felt like giving up because, as he said, "I can't stand it any longer."

The precipitation of his need to return to the hospital was a combination of a job promotion, his mother's and sister's having breasts removed for carcinoma, and the mother's moving away from his house. He whiningly and constantly asked for support and reassurance and had an intense dependency and need for close relationship with a strong parental figure. The more successful in life this patient had become, the more dangerous the world seemed to him.

In the stress interview of the first day, the content of his biting, aggressive impulses, with particular reference to his immediate family, was discussed by the stressor with some references to homosexuality, cunnilingus, and fellatio. Although the psychiatrist made strong interpretations, his attitude was accepting, and he listened patiently to the subject's catharsis. Thus, the patient seemed to be obtaining slight relief. Some anger developed toward the psychiatrist for making interpretations, but anxiety was mostly in relation to guilt over biting impulses. The emphasis on the second day, again, was on content in that the stressor implied that possibly the subject really did have heart disease. The tone was harsher and less therapeutic, and, although the subject pleaded for reassurance, he received none. There was some moderate denial and substitution of other hypochondriacal complaints, but there was no letting up in the indication that the somatic complaint was real. The patient developed moderate anxiety and some anger, which was converted to tears.

On the third day the stressor planned to overcome the patient's defenses against his phobia and brought in a dog which represented a possible carrier of rabies. His attitude was provocative and accusatory, as well as threatening and depreciatory. There was an immediate response of anger on the part of the subject, but he desperately strove to control himself and managed very well

throughout the interview, clenching his teeth and cursing mildly. In the period after the stress interview, failure of control developed, and there was an eruption of strong anxiety.

This patient experienced high levels of affective response throughout the entire experimental period, culminating on the last experimental day with the direct confrontation of a dreadful phobic object when a stray dog was brought into the room. An important feature in this case involved the wide variety of defenses utilized by the patient to avoid free anxiety. When confronted by the dog, he strove to master the situation and became quite angry, but this was soon replaced by depression. The interviewer refrained from support of the subject's attempt at mastery, and this tended to make the ensuing experience one of failure.

III

In our experimental design we had planned to increase the severity of the stress stimulus on successive days, hoping that corresponding increments in the activity of other systems would occur. At once it became clear that, no matter how much we knew about an individual subject and his apparent psychological vulnerability, we could not control the degree of induced anxiety. With a variety of tactics, including interpretations, direct psychological assaults, playing of attitudinal roles, or distortions of communications, we could not grade the stress stimulus with any degree of accuracy. Therefore, we did what we could on each experimental occasion to evoke anxiety and used the results therefrom for our essential data. In a later paper, we shall discuss the relation of the method used in the stress interview to the results achieved.

We were agreed at the outset that the estimate of stimulus intensity would not be used as a criterion of stress, since in our conceptual model stress is considered to be the effectual disturbance in equilibrium produced by an appropriate stimulus acting on a susceptible subject. Yet it may be of interest to compare generally and crudely, without statistical data, what the stressor thought he accomplished with what the observers rated they saw or heard actually was done. Such a comparison must be exceedingly crude because the time span of each set of ratings was quite different, the stressor was concerned only with evoking anxiety, whereas the observers rated anxiety, anger, and depression, and the stressor was a participant-observer, whereas his concealed colleagues were only observers.

As could be anticipated, there was excellent agreement between the stimulus-intensity ratings and the anxiety ratings for the "during" period, when stressor and subject were engaged in a face-to-face transaction. At this time the ratings of both stressor and observers were based on transactions during an identical period. No matter which technique was used, there was excellent agreement in ratings of stress intensity and anxiety during most of the first experimental day, although they were not as high as on subsequent days. Then the subject and stressor had their first contact, and the psychiatrist was engaged in probing for the patient's vulnerable spots. Since the patient was an unknown whose feelings did not yet affect him, the stressor was often uninhibited in his provocations, but nevertheless was feeling his way in strange territory. The affect seemed to carry over to the pre-period of the second day, indicating the long-time effect of the first stimulation.

Stimulus-intensity ratings for the second day correlated well with observers' ratings of increase in anger during the experimental period. The patient then knew the psychiatrist better and could permit himself to be more defensively angry at him, thus frustrating the stressor, with the result that he tended to press harder, ending in a mounting cycle of anger in the subject. Correspondingly, all ratings tended to be higher than on the first day.

On the third day the stressor tended to ease his stimulation, for this was the last day of the experiment and the role of ther-

apist in the experimenter became more overt, since he wished to return the subject to the therapeutic milieu of the nursing unit, if not improved, at least not harmed. Although this was largely an unconscious process, the stressor's ratings and the observers' ratings usually reached a consensus that the third day was the least stressful.

Prior to the experimental procedures, subjects were classified under categories of personality traits and strengths, including ego strength in relation to anxiety. During the experiments the stressor rated his stimulation higher in subjects with weakest ego strength, but the observers did not find the emotional responses were generally greater in those subjects. It seems, therefore, that the stressor's knowledge of the subject's ego strength not only influenced his higher rating of the severity of his stimulation but perhaps also weakened the intensity of his actual attack on the subject's conflicts or defenses. Speaking broadly, the sicker the patient, the more the stressor tended to pull his punches, whether he intended to or not.

In this paper we have discussed the difficulties in creating or augmenting emotional responses to psychological stimulation even in patients whose latent anxieties and crippling neuroses were conducive to the experience of anxiety. The basic stability of the neurotic organization is associated with a high degree of defense against further disturbance. These patients were sick enough to be hospitalized for treatment; yet their resistance to emotional disturbance was striking. Our experience is the opposite of the overcautious attitude of many psychotherapists, whose interpretations are so guarded lest they weaken defenses and expose vulnerable conflict areas. We found that deliberate attempts to do so were extremely difficult and rarely evoked serious responses. It seems to us that the patient's implicit role of accepting all communications from the psychiatrist as therapeutically helpful is the most important single factor in controlling the anxiety response, although other, previously mentioned conditions also contribute. When the experience of anxiety is urged and provoked under conditions of contact with a psychiatrist, it may be uncomfortable, but it frequently seems to be conducive to rapid mastery.

This may not be true in all settings and may apply only when an interested research group gives the subject considerable attention over a long period of time, within a hospital therapeutic environment. At any rate, stress research groups need not be timid in provocative stress interviews, keeping in mind the unpredictable differences in individual subjects.

Summary and Conclusions

We review our experiences with an anxiety-producing stimulus interview as part of a psychosomatic research program. The original intent of the experiment design involved an attempt to produce stepwise augmentation of anxiety responses over three experimental days, following a preexperimental day of acclimatization in the laboratory in subjects actually anxious or anxiety-prone. In actuality, no such gradations in responses developed, and it became apparent that the stressor-patient relationship was more complex than was originally realized. Both the interviewer and the subject utilized a wide variety of explicit and implicit roles within the experimental transaction. At times it was necessary for the interviewer to function as a helpful psychiatrist when the patient became too anxious. Often the subject tended to view the experiment in a helpful context no matter how threatening the interpretation made to him. Paradoxical reassurance from the stimulus interviews was a surprisingly common occurrence. The patients used other aspects of the procedure, such as a perceptual discrimination test or the drawing of a blood sample, either to obtain support because of their concern about the stress interviewer or as a check against too severe a response. It was necessary for the stress interviewer to use a wide variety of information in planning his strategy with the patient, but events shifted rapidly and the

field was so complex that predicted stimuli did not necessarily work in the expected direction.

Vignettes of several cases are presented to illustrate the stimuli utilized in the attempt to evoke anxiety and the methods adopted by the patients to cope with this stress. In the final analysis, of course, it is the response of the subject that determines the effectiveness of any stress procedure. Our results highlight difficulties encountered in making the anxiety-stimulus interview effective, in controlling its severity, and in quantifying it in a life situation.

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A Contribution to the Psychology of Schizophrenia

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In this inquiry into schizophrenia, the focus will be on the internal organization of the personality and on the manifestations of this organization that can be inferred from observations of the "psychotherapeutic" (and other types of human) relationship with the "schizophrenic." Accordingly, this analysis will concentrate on relatively more abstract features of schizophrenia than those associated with the presence or absence of "symptoms" and the allied notion of social adaptation. The latter notion is considered to be particularly distracting, since the very importance of the value judgments inherent in social adaptation and its failures makes it difficult for one to remain uninfluenced by them and to apply one's interest to other facets of the problem. For the sake of clarity, I want to state also that considerations of the phenomenology, genesis, and "symbolic" meaning of psychotic symptoms will also be omitted in this study. The chief theoretical concepts which will be used will be those of object-relationships (i. e., internal and external objects) and the capacity to form and use abstractions (i. e., the differences in the ego's attitude toward concrete objects and abstract symbols).

"Schizophrenia" as Deficiency State in the Adult with Respect to Internal Objects

Psychoanalytic work on the problem of schizophrenia so far has dealt predominantly with the nature and meaning of the symptoms (manifestations) characteristic of this syndrome. The theory of schizophrenic symptom formation provides a good account of the nature of this process.[18,24] Important and valuable as this aspect of the theory of schizophrenia may be, we shall not be concerned with it in this essay. Instead, we shall focus on a more abstract quality of the general psychological organization of persons who, under given circumstances, may or may not manifest psychotic (or other) "symptoms." This point of view, namely, to regard symptoms as the manifestations of a disturbance in a human situation rather than as something "inherent in a disease," is consistent with the psychoanalytic philosophy of the study of human living. Indeed, much of what follows will represent a synthesis based on the work and findings of numerous other investigators.*

Process of Growing Up Viewed in Terms of Object Relationships.—To begin with, let us take a brief glimpse at the psychological process of growing up. This could be described most concisely by stating that it consists of the building up (within the ego, as well as in the process of interaction with it) of large numbers of internal objects. The origin of this notion we owe to Freud and his concept of superego formation. The process which we have in mind, however, is a more general one, and, according to it, the ego itself is composed

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* The psychoanalytic aspects of the theory here put forward were influenced chiefly by the works of the following: Eissler,[11-14] Fairbairn,[15] Kasanin,[28] and Wittels.[79,80] In addition to these, the recent writings of Hoedemaker,[24] Pious,[60,80] and Wexler[75,76] were helpful in organizing the thesis presented in this essay.

of introjected objects.† To ensure healthy development, the objects to be introjected must, first of all, be available; and, secondly, they must be so constituted that they will tend to favor "autonomous" ego development, on the one hand, and be adequate for coping with the complexities of civilized living in a modern industrial society, on the other.

Such a view of psychological growth in terms of the acquisition of "objects" (and, of course, of making them one's own) is, in a way, analogous to physical growth as a process of tissue building. In the latter, the continuous change from infancy to adulthood (and after) represents, from the physicochemical point of view, the taking into the organism of external "tissues" and their assimilation into one's own. Thus way the infant's body grows (literally). In adulthood, literal growth ceases, but a steady process of physicochemical transformation continues. It seems to me that we might well regard the development of the "personality" in a similar manner. While the body feeds on food, the personality "feeds" on objects. It need hardly be added that this is an abstraction, since in human life, as we know it, there is no such thing as the one without the other. The Bible says, "Man does not live by bread alone." This reminder was, and continues to be, necessary because man's interaction with his (nonphysical) "human" environment is less concrete, and therefore more elusive, than is his contact with inanimate bodies.

Returning to the growth process, we could summarize the essential features of it as follows:

1. The acquisition (internalization) of objects
2. The "assimilation" of the objects into the ego (and self)
3. Learning how to relinquish objects and to acquire new ones

All three of these, in various measures, are necessary for the development of the personality in that particular way which we consider "human" in our culture. The synthesis of (adequate) internal objects into a harmonious whole is necessary in adult life for more or less satisfactory living.[80] The disparities between the "realities" of inner (old) and outer (current) objects constitute, in one sense, "neurosis."[37] Viewed in this light, "neurosis" must be regarded as "normal" for adult human living, insofar as the existence of a rich source of inner objects must unavoidably lead to some disparities between these and current human relationships. Optimal psychological "health"—in this frame of reference—consists of the ability to make the necessary discrimination in regard to the foregoing disparity of human object relationships. Without this, the acquisition of new objects is hindered by the presence of older ones. At the same time, our concept of the "ideal" personality demands a measure of stability and permanence in regard to certain objects (e. g., mother-father, wife-husband, etc.).‡

† In this I follow the ideas of Fairbairn and Wittels. In classical analytic theory the superego is essentially the only (personal) internal object. I believe that the formulation of schizophrenia as a deficiency or defect of the superego, such as was proposed by Pious[60] and others, may stem from an attempt to fit the observations obtained in the therapeutic situation with the schizophrenic into the classical theory. This is undesirable mainly because Freud's original concept of the superego refers to an internal object typical of the "normal-neurotic" adult. The superego is an excellent concept, but its value would be only impaired if it were extended to include the processes of ego building proper.

‡ Clearly, what is referred to as the building up of internal objects describes the same phenomenon as what has been known in analytic theory as "identifications" (e.g., the developing child "identifying" himself with mother, father, brother, etc.). If identification is used in this sense, the notion of introjecting external objects and so building up internal ones is synonymous with it. However, the concept of "identification" is also used in another sense, namely, to describe a much more complex and genetically "later" psychological operation, such as occurs when we put ourselves, so to speak, into someone else's position. In this way, we "identify" with him, yet retain our own, preexisting identity. Finally, the fact that the expression "to identify with someone" . . . connotes an active process on the part of the ego—rather than something that hap-

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The "Schizophrenic" and the Child.—It seems to me that most instances of "schizophrenia" are best understood as representing a state of deficiency of (adequate) internal objects in an otherwise adult human organism. This makes for certain basic similarities between the schizophrenic and the child, which have been noted by many authors. However, the differences between the two should not be slighted, lest we make a connection between them not unlike that between a cachectic adult and a child based on the mere fact that both are of the same weight. In other words, while the schizophrenic suffers from a deficit of internal objects, he is physiologically usually mature and his personality organization usually differs in various ways from that of child. Last but not least, the social structure in which the child and the schizophrenic adult live, or are expected to live, differ in exceedingly important ways.

A theoretical approach to schizophrenia in the foregoing terms is advantageous for several reasons. It helps to cut across the accustomed nosological lines. The traditional diagnostic categories of schizophrenia are based on the phenomenology of symptoms (including "affects" and other criteria) and on social judgments. Accordingly, they may be helpful in determining when social action should be taken toward a particular person and when it need not. At the same time, traditional nosology, as is so often emphasized—without, however, anything being done about it—places a tremendous barrier in the way in our attempts to arrive at a scientifically more accurate and socially less biased assessment of certain types of human behavior.

It should be evident that not necessarily all persons "nosologically schizophrenic" will be found to have a (developmentally determined) deficiency of internal objects, although this would probably be true in most cases. On the contrary, the symptomatic concept of schizophrenia is far too narrow as a notion under which all adults relatively poorly endowed (or deficient for other reasons, such as severe regression or organic brain damage) with internal objects could be subsumed. It is not advocated that our view of schizophrenia necessarily be broadened so as to include all these concepts. We merely want to establish some connections between the structure of internal objects and the ego's ability to relate to abstractions (i. e., the power to form and use symbols). Furthermore, this approach will enable us to make significant connections between the nosologically schizophrenic and the socially normal (nonschizophrenic) person.

Evidence in Support of the View of "Schizophrenia" as Deficiency of Internal Objects

A manifest schizophrenic breakdown is usually precipitated either by the loss of an external object or by the need to make a significant relationship with such an object. Let us analyze the nature of these events in some detail. The loss of an object is a general and fundamental sort of "trauma," perhaps comparable to starvation in the physical realm. The healthy adult organism can, of course, withstand the lack of food for a relatively long time. Similarly, object loss is painful but bearable, as a rule. What makes it bearable? The process of mourning is a familiar one and requires no comment. We take for granted, of course, that mourning can occur only in a relatively well-developed personality. A crucial phenomenon in the process is the abandonment of an external object relationship and the (temporary) substitution for it of an internal object relationship (i. e., between the superego and the ego). Mourning is thus made possible by the very existence of a latent inner reservoir of objects

pens as a result of an interaction—makes this concept, expressed in this way, somewhat misleading when we refer to early ego development: The latter cannot be predicated upon the very "system" (ego) which is in the process of creation. According to this formulation, an ego is necessary for "making" identifications, while, at the same time, the ego is being made up (in large part) of "identifications."

upon which the ego can draw in the case of need (much like stored glycogen, fat, and muscle protein as inner sources of food upon which the organism draws during periods of starvation). The occurrence of a schizophrenic break in the face of the loss of an external object might be regarded as evidence of a lack of "stored objects" (if such terms are permitted). As a matter of fact, we are accustomed to interpreting certain types of gregariousness in human relationships as protection on the part of the ego against an inner "emptiness."

Internal Objects and "Fantasy Objects." I believe we should regard hypochondriacal preoccupations and psychotic delusions and hallucinations in a similar manner: They are "objects" for the ego's interest.[66,71] The ego can function and, so to speak, experience itself vis-a-vis these substitute objects (i. e., the body, "fantasy objects," etc.) and can thus stave off "nothingness" (death, dissolution, aphanisis[36]). It must be noted that what we call "fantasy objects" are by no means the same as internal objects. Internal objects are always historically derived from external objects, and the process of internalization is, accordingly, something that originally happened to the ego in a passive way. "Fantasy objects," on the other hand, are not so derived, but originate from the ego's own defensive, self-reparative struggle and creative effort.§ An inner appreciation of this difference between these two types of "objects" is postulated. "Fantasy objects" are readily given up when (real) external objects become available to the ego. Internal objects, on the other hand, are often never given up at all, or are relinquished only slowly and gradually.

How Do We Make Inferences About the Ego's Relationship with Objects? "Models," "Transferences," and Affects.—We might digress here and comment briefly on the ways in which we can infer the nature of the ego's relationship to objects. One of the best methods at our disposal lies in observations based upon the patient's response to the psychotherapeutic situation. We thus speak of the immediate and intense "transferences" which the schizophrenic makes to the physician. On the other hand, we know that in the neurotic the development of a transference neurosis toward the analyst is a slow process, which unfolds, with its various ramifications, only gradually as the resistances to it are analyzed. It is somewhat misleading to speak of "transference" in the first case, since it is a significantly different phenomenon from that occurring in the neurotic. In other words, by transference we usually understand the patterning by the ego of a relationship to an external object on the model of a preexisting relationship with an internal object; the latter, in turn, is derived, at least in large part, from a relationship with an external object. It follows that if there is a lack or relative deficiency of internal objects, transferences (in the foregoing sense) cannot occur. This, of course, does not mean that no human relationship can develop, as was Freud's early impression of the "narcissistically isolated" schizophrenic. The relationship which develops in such situations has sometimes been designated as a "real" relationship to the therapist, in contrast to a "transference" relationship. This name is exceedingly ill chosen, inasmuch as it fosters the idea that there is something "unreal" (make-believe, etc.) about the transference. I would suggest that we call this type of ("real") relationship a "model relationship." This name is based on the fact that the object of such a relationship functions for the ego as a model (example) for introjective learning.[19] The prototypes of such relationships would be that of the small child vis-a-vis

§ Although the term "fantasy object" is newly coined, the observations to which it refers have been described in various ways by others. Rosen, for example, speaks of the "reality of schizophrenic 'imaginations.'"[67] Rycroft, in a recent paper, seems to describe a very similar concept when he speaks of "pathological idealization" as "the result of a defensive hypercathexis of imagos produced by splitting of introjected external object imagos and their later imaginative elaboration."[60]

his mother, father, and older siblings. Similarly, the schizophrenic's relationship with the therapist is a "model relationship." For a vivid illustration of this phenomenon I shall quote from a paper of Numberg's, in which he described a phase of a schizophrenic patient's recovery as follows [44]:

> He became interested in the outside world, in political events; he read a great deal, learned other languages, and busied himself in the ward. However, the striking feature was that he wished to work under the direction of a superior, to take orders from him and execute them dutifully. "I will carry out all orders and submit to them completely," he protested. He submitted to my authority, felt helpless and dependent on me, asked for orders and commands from me on how he ought to behave. "You must teach me how to do everything," he told me.

The patient here verbalizes his wish and need for a model upon which to base his ego organization.

For obvious reasons, model relationships are of greater importance during the earlier periods of human life, and transference relationships become more significant as we grow older. Model relationships, however, never cease to play a role, and a certain amount of learning takes place in this way throughout life.

The two types of human relationships designated as "model" and "transference" relationship correspond, it seems to me, to two fundamentally different ways of learning. The first leads to learning by example, or by "identification"; illustrative of this process is the child's learning his mother tongue. In contrast to this, a relationship based on "transference" implies abstraction, comparison, and logical discrimination: It leads to learning by understanding, and the methods of logic (and science). Illustrative of this process is the learning of the scientist. Significantly, this is based on a conceptual chain of events consisting of observation - inference - experiment and/or new observation, etc.; this type of learning does not require the presence of another person as a concrete object. Although in actual life—for example, in school situations—the foregoing two types of learning experience usually occur simultaneously, a clear distinction between these processes would probably be helpful for a better understanding of the psychology of education (cf. Polanyi [51]).

Regarding the concept of "transference," it is clear that model relationships form the bases upon which later transference relationships rest. Yet it is also not altogether incorrect to speak of "transference" in the schizophrenic, for two reasons: 1. He is not completely devoid of internal objects, which are predominantly "bad". 2. In a somewhat wider sense of "transference" we might also speak of the patterning of the ego's relationship to the new model object on the basis of its former relationship with fantasy objects as "transference." This phenomenon seems to be of considerable importance in schizophrenics, and also to a less extent in others more richly endowed with internal objects.

Another important method by which we can make inferences regarding the nature of the ego's relationship with objects lies in observations about the person's emotional (affective) experiences. We are justified in regarding affects, from this point of view, as indicators of whatever the state of affairs between ego and object [29,30,70] happens to be at a particular time. Anxiety thus "means" that the ego feels threatened by impending object loss; mourning signifies that the threatened loss has occurred and is acknowledged by the ego, and pain, for example, indicates a certain kind of relationship between ego and body (as object). Accordingly, the emotional impoverishment or affective "dulling" of the schizophrenic would lead us to conclude that this phenomenon is an indication that there is a deficiency in the number and the range of objects available for interaction with the schizophrenic ego. In other words, (true) lack of affects signifies lack of objects.‖

‖ For a similar view of this phenomenon formulated without using the concept of object relationships, see Arieti. He writes[3] (page 308): "When the patient loses his common symbols and

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Some Connections Between Social Situations and Schizophrenic Symptoms.—It remains for us to comment on the mechanisms by which the need to make external object relationships may precipitate overt schizophrenic symptoms. We conceive of the schizophrenic, when he is in a socially and psychologically relatively well-compensated state, as being able to form relationships with external objects only of the "model" variety. The object suitable for this type of relationship is not too readily available, since it requires a special sort of orientation on its part toward the "schizophrenic." In order to establish a manageable relationship with most people, it is necessary that the adult ego should know how to conduct itself with respect to the object's specific psychological needs and social requirements. This "knowledge" is based on previous human relationships of a more or less similar nature, which serve as models for later relationships. The lack of such internal models (objects) explains the difficulties which arise with the need for human relationships at a later time. By the same token, faced with such a need, the ego is confronted with what appears to it as a task which it is ill equipped to handle. It is in this way that the previously compensated state may give way to an overt psychosis; the latter is the restitutive defense against the ego's confrontation with its lack of (adequate) internal objects and its realization of "inadequacy" in interacting with people. This process may be likened to calling someone's bluff in a poker game.

The onset of symptomatic schizophrenia in early adult life, when the socially grown "child" must leave home and make contact with others, is consistent with the foregoing considerations. Only by deemphasizing symptoms, and their usually catastrophic social consequences, can we pay adequate attention to the nature of human relationships in the life of schizophrenics. The latter tend to be obscured by focusing on precipitating causes, genetic predisposition, or mechanisms, although all of these must be taken into account for a comprehensive picture of "schizophrenia." Finally, we may conclude that not only does individual (e. g., sexual) or social (e. g., choice of occupation, marriage) pressure toward object-contact function as a "stress" pushing the person closer to overt schizophrenia, but, contrariwise, simple and well-structured social situations (e. g., religious orders, military organizations, etc.) tend to protect him from it.

Connection Between Object Relationships and Symbol Formation

To describe and explain psychological phenomena in terms of object relationships is a mode of thought that is becoming increasingly familiar to psychiatrists and psychoanalysts. This material can now be brought into connection with notions about symbol formation, the capacity for abstraction and related ideas. The latter concepts, too, are familiar to many workers in the psychological field. Many of these concepts, however, have been developed by philosophers and have remained relatively isolated from psychoanalytic theory. It is not within the scope of this essay to develop the connections between "objects" and "symbols" in detail. Only those aspects which pertain to our present inquiry into the nature of "schizophrenia" will be considered.

The best criterion for differentiating between man and the higher mammals is the specifically human capacity for abstraction. This capacity finds expression in language, ego formation, organized memory, culture, science, and numerous other manifestations based on symbols.¶ This psychological capacity is made possible by, and has developed in the course of evolution concurrent with, the growth in size and complexity

therefore desocializes himself, it is impossible for him to have any emotional reaction to these common symbols. In other words, he does not repress the emotions; he cannot experience them."

¶ For a comprehensive presentation of this approach to the nature of human experience, see the works of Cassirer,[7,8] Goldstein,[26-28] and Langer.[32,33]

of the frontal, and to a less extent, the temporal lobes of the brain. In other words, we would be justified in saying that what is specifically "human" about man is the development of the frontal lobes, the ego, and the ability to make and use symbols, including those of language. The foregoing statement describes a complex subject from three complementary frames of reference: 1. The frontal lobes refer to anatomical, physiological, and physicochemical matters. 2. The concept "ego" implies the notion of object relationships and constitutes the frame of reference of psychoanalysis. 3. Lastly, the frame of reference of symbolization deals with our subject with the methods and concepts of symbolic logic, semantics, and modern philosophy.[17,54,61]

There is a compelling linkage between object relationships and symbols along the following lines: The behavior of the young child, until the age of the beginning of speech, can be reproduced in most respects by chimpanzees reared like human infants. The life of this presymbolic organism is characterized by an immediacy of all experience. This is often described by saying that for the small child there is no past and no future, but only a present. The abstractions of "past" and "future" and the differentiation between the "possible" and the "real" are not present at this stage of development.[43,46,47]

Further, we can observe a parallelism in the growing child between the development of object relationships and the increasing capacity for abstractions. It seems to me that this is neither simply a fortuitous coincidence nor a mere parallelism of a complex development viewed from different points of view. Rather, it appears that we are dealing with a genuine interdependence of biological functions in such a way that the development of one function facilitates, and is necessary for, the development of the other, and vice versa.

Abstraction; Delay; Long-Circuiting.—How does the capacity for abstraction develop? It is generally assumed that the power to form symbols arises *pari passu* with "psychological development." In other words, this function is thought to develop, like many others, as a part of our genetic (in the physical sense) heritage. Now it seems to me that the evidence strongly suggests that the formation of stable ("good") internal objects is a prerequisite for symbol formation. The "survival" of the ego depends, as has been mentioned, on contact with objects. At first this must be contact with properly supporting external objects. If this and similar contacts are satisfactory, they will be introjected into the ego, and in this way the latter becomes relatively independent of (more or less) continuous contact with external objects. Instead, the ego will be able to tolerate separation and distance from external objects, and it will be buttressed in this ability by its now inviolably intimate and secure contact with internal objects. The very "reality" and security of the ego's relationship with its internal objects makes it possible for it to enter into a more tentative and discriminating contact with external objects. It will thus be able to deal with external objects not only as "immediate objects" but also as abstractions, represented by symbols. The basic symbols which carry and embody the objects which they represent are, of course, pictures (images) and words.

The phenomena which we have described above have been considered by neurologists from the point of view of the evolution of nervous organization, from the simple reflex arc of lower animals to the complex long-circuited central nervous system of man. Accordingly, in the three complementary frames of references mentioned, frontal lobes, ego, and symbols could all be viewed as mechanisms which enable man to transcend the immediacy of his concrete experiences and actions. It is in this fashion that a distancing between experiencing organism (self, ego), on the one hand, and representation (symbol) of experience, on the other, comes about. The frontal lobes, as a colossal synaptic switchboard, form the structural basis for a delay of inpulses (messages in terms of electrical and chemi-

cal events). Similarly, the building up of internal objects in the ego enables the latter to wait—to experience a delay in responding to needs and stimuli. Finally, symbols, too, are regarded as intermediates between concrete objects, on the one hand, and action, on the other; in this instance, representation and abstraction (whether in imagery, thought, etc.) is a measure of "long-circuiting."

Symbolization of Objects and Concrete Use of (What Appear to the Observer as) Symbols.—What evidence justifies the postulate that the formation of adequate internal objects in the early ego is a prerequisite for the development of the capacity for abstract thought? Clearly, the most important information would have to come from observations about the nature of symbol formation in children (or adults) who have been deprived of external objects and are therefore deficient in their ego organization of internal objects. A few children have allegedly grown up under almost totally nonhuman conditions, like jungle animals. According to reports, these children were much like animals and possessed no power of speech.[43] The development of symbols is thus not based simply on an inborn, genetic mechanism, like the proper development of the teeth, tongue, and other "organs" of speech. It depends upon a properly "human" environment.

It was suggested that we look upon "schizophrenia" as a deficiency of internal objects. Observations regarding the ability to form and to use symbols in such persons would thus also serve as an important source of evidence regarding the connection between "internal objects" and symbols. Indeed, we find that schizophrenics manifest significant deviations in regard to language and other symbols as compared with "normal adults." They do not treat (what to the observer are) symbols as abstractions but, rather regard them as concrete, "real" objects.[3] This fact is consistent with our thesis that the presence of internal objects is a requisite for the proper use of symbols on the part of the ego. Beyond this, it illustrates that some symbols (words) may be used in an "imitative" manner, and in this way they can serve the same protective function for the ego as do "fantasy objects." Lastly, such "objects" are made, so to speak, with the help of the nonsymbolic, concrete use of language and imagery (e. g., "delusions").

On a higher developmental level, the interconnections between objects and symbols is more intricate. Not only do internal objects potentiate the acquisition of symbols, but the learning of symbols further facilitates the ego's relationship to new external, and ultimately new internal, objects (experiences). A more detailed examination of this process must be postponed for another occasion. It should suffice to note, at this time, that this process of mutual facilitation appears to be of the greatest importance for the understanding of the (relatively) rapid growth of culture and of science. It also has important bearings on the psychological nature and function of "theory," stemming from the fact that abstract conceptions can function vis-a-vis the ego in a manner similar to internal objects. Both the power of theory for mastering "external reality," as well as the dangers inherent in abstractions as substitutes for concrete objects, derive from this fact.

Analysis of Processes by Which the Schizophrenic Is "Changed" by Major "Therapeutic" Techniques Currently Employed

Efforts to influence the (behavioral) state of schizophrenic patients are usually divided into two large categories, called psychotherapy and physiological therapies. We shall consider them in this order.

The common denominator among the psychotherapeutic approaches lies, obviously, in the fact that the effort to help the patient rests on his being brought into contact with the person of the therapist. The exact ways in which this is "therapeutic" has received a great deal of attention

from psychiatrists and has led to a multitude of "explanations."[4,65] The chief reason for the foregoing situation, it seems to me, is to be found in the close connection between the notions of "psychotherapy" and a logical, verbal exchange between patient and therapist. Redlich,[52] for example, states (page 30):

> However, no generally accepted theory accounts for vast differences of approach in the psychotherapeutic process with schizophrenics, varying from rather different ego-supporting approaches to the direct id-interpretations of Rosen, from vigorous manipulation of the patient to marked passivity of the therapist.

It seems to me that we should consider the possibility that it is not so much the foregoing "treatments" that are different, but, rather, that we have come to describe processes with significant common features in markedly different ways. In other words, I suggest the possibility that it is not the actual operations of the "human relationship" between therapist and schizophrenic patient that vary greatly, but only the ways in which we have become accustomed to describe these therapies. Perhaps we are saying the "same thing" in many different languages—and do not recognize this state of affairs because we mistakenly identify different linguistic forms with different "meanings."

Another serious objection to describing various therapies as "ego-supportive," "uncovering," "active," "passive," etc., lies in that these terms all refer to what the therapist aims to do. Therapy is thus characterized in terms of the therapist's intent, and not in terms of the actual operations which occur in the relationship between patient and therapist.[67] For the latter, the real meaning and impact of the therapist's activity on the patient must be known and taken into account. Only in this way can we avoid the ambiguities that result from the many well-known instances—which hardly need be documented further—in which what seems like "passivity" to the therapist has some very "active" meaning to the patient, or of situations intended to be "ego supporting" having no such effect.#

In psychoanalysis—the model of all modern psychotherapies—it is taken for granted that the patient's "free associations" and the analyst's "interpretations" are of crucial significance in the therapeutic process. And so they are. We must remember, however, that the analytic process proper requires a well-developed ego on the part of the patient, and that it is a process largely based on, and utilizing, abstractions (mostly in the form of linguistic symbols) as a means of establishing contact between two human beings.

It is the utilization of the conceptual framework of abstraction and logic which leads to the apparently paradoxical state of affairs in which we are confronted by a number of different psychotherapies—in the logical content of their assertions each extremely different from the other—yet each of which appears to be helpful (to a point) for the patient. In other words, the questions which we want to answer are the following: How is it possible that the "logically" (and contextually) different approaches of Federn,[16] Fromm-Reichmann,[22] Rosen,[56] Schwing,[62] Sechehaye,[63] and others[5] are all helpful to the schizophrenic? Is one of these approaches more and another less correct? What is the relevance of their logical propositions to the so-called "disease process" at hand? What is the mode of operation of these therapies?

Object Contact with the Schizophrenic.—The idea that what is relevant in the therapeutic contact between the schizophrenic and his therapist is somehow the object relationship itself, and not the "verbal communication," is by no means novel. Indeed, this is sometimes claimed for the "analytic situation," too, and in this way the entire theory of psychotherapy becomes muddled and confusing. A clarification of what is meant by the therapeutic effect of the "relationship itself" is badly needed.

See in this connection Szasz and Hollender.[73]

The notion of "nonverbal communication" with the schizophrenic also refers to what I am discussing here. An unfortunate dichotomy often arises, in this connection, between verbal and nonverbal communication, so that the latter becomes equated with that which has an "emotional" impact on the patient, and the former with that which has a merely "intellectual" effect. The juxtaposition of these concepts and modes of experiencing is grossly misleading. As I see it, in the presymbolic state (e. g., a small child), living in concrete action and its inner representation predominantly by "feelings" constitutes both the emotional and the intellectual aspect of the organism's experiences. Similarly, for the adult for whom symbols are meaningful, verbal language is not an intellectual expression only, but is equally as much an expression of emotion. The words "emotional" and "intellectual" serve us best as a means of subdividing experience. These terms are often used, but should not be, as denoting levels of organization, with the implication that "emotionality" is more primitive and "intellectualism" more mature. It is in this way that the myth that the mature adult is less emotional than the child arose. It would seem more consistent with the facts not to speak of emotionality as "more or less"—as if it were a matter of quantity—but, rather, to try to comprehend the different ways in which organisms of diverse organization experience emotions.[12,43] The adult is, accordingly, not less emotional than the child, but is emotional in a different way; and, as a matter of fact, if we think of emotions not in terms of whether they overcome us, or not, but in terms of their range, (i. e., variety, subtlety, complexity), then we realize that the adult would have to be regarded as more, and not less, emotional than the child.

We have suggested that the schizophrenic is deficient in internal objects, whereas the "neurotic" is not. The need arising from this is one for external objects suitable for introjection. This would constitute the natural reparative tendency of the organism. It is important to note that people with whom the schizophrenic comes into contact in the course of "normal" social intercourse are not available as objects for the type of interaction which he requires. I would compare this situation with the psychology of child-raising. Most people like children, in a vague and general way, but would not be interested in raising a strange child just because the child needs a parent. Adults seek most of their human contacts on "another level." In any case, there must be a reciprocal need in the adult toward the child in order for it to function as a parent. Generally this is not a problem, since this reciprocity of needs flows directly from the adult's need to take care of himself, which is readily displaced onto his own child.* Similarly, to treat the schizophrenic, the therapist must have a need of his own to make contact with, and to devote himself to, the patient.[13] This reciprocity of needs, and this alone, would make the therapist available to the patient as an object for introjection. However, this in itself is not enough. I would add to this, that the therapist must show the patient by example how he himself deals with the world (this includes his own impulses, as well as his orientations and techniques of relating to other people and inanimate objects). In this way the patient gains access to that prototypal experience from which he was deprived in childhood, namely, to learn how to deal with the world by introjecting adequate objects. This process is often called simply "love." Unfortunately, this one word is used as an abstraction of so many

* I ask the reader's indulgence of this and other similar oversimplifications. In a study of a problem which is as poorly circumscribed as schizophrenia is today, one cannot help touching on numerous issues subsidiary to the one or few themes which can be developed in a short paper. Faced with such a problem, one might disregard subsidiary issues altogether, digress into more or less detailed discussions of them, or aim at some compromise between the two extremes. I have chosen the last course, in most instances, thinking that a brief statement of my position regarding the issue in question would mislead the reader the least.

diverse experiences that an explicit analysis of its meaning in discrete contexts is a necessity for work which aims at scientific, rather than sentimental, appeal.

Communications with the Schizophrenic Are Not in Form of Logical Propositions.

The foregoing conceptions have far-reaching implications for the problem of the logical diversity of various psychotherapies used with schizophrenics. As we have noted, not only is the schizophrenic deficient of internal objects, but he is also unable to use abstractions (symbols).† It follows, therefore, that what may have various abstract meanings to us, as psychiatric observers, may have no such meaning to the patient. The fact that the patient "listens" to what is said to him, that he appears to accept it and even may make the interpretations his own, has no bearing on what we consider, in other situations, as the validity of logical propositions.

It is important to note, in this connection, that the ability to deal with "logical propositions" (in the sense of symbolic logic[54]) does not normally develop until some time after the 11th or 12th year of life. Piaget describes four stages in the "psychological development of operations," the final stage being that of "propositional or formal operations." He states[45] (page 18):

> The final period of operational development begins at about 11 to 12, reaches equilibrium at about 14 to 15 and so leads on to adult logic. The new feature marking the appearance of this fourth stage is the ability to reason by hypothesis. In verbal thinking, such hypothetico-deductive reasoning is characterized, *inter alia*, by the possibility of accepting any sort of data as purely hypothetical, and reasoning correctly from them.

If we agree that in the interaction between therapist and "schizophrenic" patient we are not dealing with logical propositions, the notions of "true and false" or "exact and inexact" cease to be relevant.[25] These concepts are applicable only to certain types of abstractions, namely, to logical propositions. They have no meaning in connection with esthetic or ethical judgments, as well as in many other contexts.[59]

The significance of these considerations for psychoanalytic theory can hardly be exaggerated. Indeed, quite early in his work Freud enunciated what is basically the same principle when he called attention to the absence of (this type of) logic in dreams. For example, two opposite propositions in a dream do not negate one another. Yet, even though these facts have long been known to psychoanalysts, there is a persistent tendency to use adultomorphic, logical considerations in trying to decide, for example, between which of various utterances "said" to schizophrenic patients are "correct" and which are "incorrect." (This is not to say that all "approaches" to the schizophrenic are equally valid and of the same benefit to the patient.) This difficulty may derive, in part, from the fact that science, by definition, is limited to the use of the logical method.‡

† An unfortunately misleading use of the notion of "symbol" has arisen in the psychiatric literature on schizophrenia. I am referring to the commonly held view that the schizophrenic "knows" symbols especially well, that he "understands the unconscious," and so forth. This is based, largely, on a mixing up of the positions and frames of reference of the patient and of the psychiatric observer. In other words, it is one thing to represent an event A by a symbol B—knowing, if necessary, that B merely stands for A—and it is an altogether different thing to equate the two. Thus, when the schizophrenic uses "symbols," he uses them in the second sense only; for example, he may regard an apple as a breast or experience the therapist as his father. Accordingly, when Sechehaye,[58] speaks of "symbolic realization," the terminology conflicts with the concept of symbol as abstraction. And it is evident in her account that the gratifications of the patient's wishes were symbolic only in the sense of their meaning for analytic theory, i.e., for the psychiatrist, but they were not symbolic for the patient. Sechehaye's therapeutic contact with the patient was characterized by prolonged contact of an immediate and "concrete" sort, such as is the rule between mother and child.

‡ We touch here on a matter which is similar in many respects to the problem of "values" and ethical judgments. Considering the relationship between science and ethics, Bertrand Russell wrote as follows[49] (page 255): "I conclude that, while it is true that science cannot decide questions of

(Footnote continued on following page)

I do not want to create the impression, however, that we cannot arrive at an understanding of "schizophrenia" or of the nature of human relationships with such patients by the methods of science. The considerations mentioned above may, however, well account for the significant fact that artists have for so long been more successful in "explaining" the psychology of the child and of the "mentally ill" than have scientists. It seems to me, rather, that scientific effort must not become fixated, so to speak, on the utterances of the therapist or of the patient (patterned after the model of the "analytic situation") but must abstract certain recurrent patterns and features from interaction with persons in this prelogical state and must then establish laws pertaining to them.

Therapeutic "Experience" Versus Theories of Therapy.—Let us apply what has been said to the concrete example of the controversy regarding various therapeutic "techniques" used with schizophrenics. Psychiatrists argue, reason, and try to decide whether Rosen's highly dramatic and aggressively verbal approach is "correct" or not, or what parts of it might be "right" and what others "wrong." His method may be contrasted with Schwing's quiet, almost silent, contact with her patients.[65] In our efforts to understand how these "mental healers" work, and what effect they have on the objects of their interest, we should compare their work to that of the artist. No one today would waste any time trying to decide whether Rembrandt's or Picasso's "method of painting" is the "correct" one.

In scientific work, "truth" is a matter of degree. In the words of Russell, again[59] (pp. 11, 12):

> Science thus encourages the abandonment of the search for absolute truth, and the substitution of what may be called "technical truth," which belongs to any theory that can be successfully employed in inventions or in predicting the future. "Technical" truth is a matter of degree: a theory from which more successful inventions and predictions spring is truer than one which gives rise to fewer. "Knowledge" ceases to be a mental mirror of the universe, and becomes merely a practical tool in the manipulation of matter.

Russell was speaking, of course, of the physical sciences; similar considerations, however, apply to the psychological sciences as well.

Let us recapitulate the chief conclusion which follows from what was said above. Insofar as we consider the problem of the relationship between therapist and schizophrenic patient from the point of view of science, we must distinguish sharply between the following two categories of events:

1. Individually specific and unique happenings take place between a particular therapist and a particular patient. The communications which pass between these two persons are, for the large part, not logical propositions.[6]§ Accordingly, the methods of science cannot be applied to the "raw material" of the therapeutic situation.

2. We can abstract certain relatively invariant features from the situation under consideration and can thus construct various theories of the process of interaction (and of the "make-up" of the individual participants themselves). From this point of view, a particular therapeutic situation will have to be looked upon as an illustrative example of a more general scheme. In our theory, for example, we have the important invariant notion that the therapist must function as an object available for introjection by the object-deficient patient. Certain "predictions" are inherent in this concept; that is, the therapist's personality will make a strong imprint on that of the patient, so that the latter will become, in

> value, that is because they cannot be intellectually decided at all, and lie outside the realm of truth and falsehood. Whatever knowledge is attainable, must be attained by scientific methods; and what science cannot discover, mankind cannot know."

§ Eissler was among the first to bring real theoretical clarity to this issue. He stated that in order to treat the schizophrenic effectively, the therapist must be able to communicate with him in the language of the "primary process."[18] This, of course, is in sharp contrast to the nature of "interpretations" used in the "primary model technique" of analysis.[6,66]

some ways, like the former. This process is, of course, similar to what happens in the course of "normal" childhood development, in that the child becomes, in part, an embodiment of those who raise him. The differences between the theory of the treatment of schizophrenics, on the one hand, and the theory of "psychoanalytic treatment," on the other, are most evident in this connection.[68,69]

We may now conclude that the differences among diverse psychotherapeutic approaches to the schizophrenic lie (chiefly) in differences in the logic of the propositions by which the therapists involved explain their procedures to themselves and to their colleagues. This does not interest the patient. The analogy with child-raising is again helpful. There are numerous diverse explanations as to why parents and educators do whatever they do with children. "In spite" of these logical differences, children manage to grow up, insofar as there are adults who genuinely "take care" of them. Furthermore, the diverse "communications," so to speak, with which schizophrenics are treated could be well compared with the child's response to being talked to or read to. We know how much children love both to be talked to or to be read to, but we know better than to attribute this to their interest in the particular narrative at hand. The French say, *C'est le ton qui fait le music.* In other words, the small child will "respond" almost equally to being read to from a children's book, a cookbook, or a collection of Shakespeare's sonnets, as long as this is done with interest on the part of the adult. Similarly, the diversity of psychotherapeutic techniques with schizophrenics is instructive not on account of any relevance of their respective logical propositions (with regard to the schizophrenic's "conflicts") but as expressions of the individually unique ways in which different therapists experience and communicate their interest in their patients. Some mothers sing to their children; some read to them, and others take them for walks. It would be patently meaningless to inquire as to which of these ways is the best one for relating to the child at that particular time. If there is a genuine relatedness—so that the child or the schizophrenic can learn by introjective identification—any one of these experiences will be valuable for the development of (probably both) the participants. How valuable such differing experiences might be cannot be rationally answered without specifying later conditions under which the person will have to live.

Some Differences Between "Therapy by Example" and "Primary Model Technique."—In summing up these considerations regarding the mode of action of certain types of object relationships with respect to the schizophrenic, a few comments about the differences between the foregoing human situations and the analysis relationship proper might be added. The similarities between the two are essentially limited to the fact that both are "human relationships." The differences seem to me far greater than the similarities, albeit these have been obscured [21] by the fact that verbal communication appears to play a role in both. The treatment of the schizophrenic revolves about remedying a lack of internal objects. Internalizations of the therapist (of his various skills, attitudes, etc.) and of others, insofar as they supply useful models for living, are encouraged. Processes which hinder such introjections are avoided (e. g., analysis of the "imitative" processes). If therapy is successful, the patient may gradually reach a stage of human existence comparable to that of the adult "normal-neurotic," who may or may not be a candidate for analysis. The "primary model technique" presupposes a capacity for abstraction in the patient. He is not in need of new internal objects. On the contrary, his relationships with external objects may cause him "pain" insofar as they are insufficiently discriminated from relationships with internal objects. The analytic process uses many symbolic operations, and a (personal) distance from the analyst is maintained throughout the treatment which is very different from the prox-

imity between therapist and patient necessary for the schizophrenic. The memories and constructions of the analysand, as well as the interpretations of the analyst, constitute, at least in large part, logical propositions. The concepts of "exact-inexact" apply to these, as do other criteria of science. The scientific method as such is thus applicable to the contents of the analytic situation. In contrast to this, science can tell us something about the process of interaction between therapist and schizophrenic, but it has nothing to say about the "content" of the interaction. This material is akin, in this respect, to art, ethics, and other aspects of human experience, regarding the content of which science has nothing to say.

Physical "Therapies" in Schizophrenia.—From the foregoing point of view, the mode of action of so-called physiological "therapies" to which schizophrenics are subjected may be summarized briefly as follows: We conceive of the symptoms of "schizophrenia" as restitutive manifestations which attempt to cover up a deficiency of internal objects. Substitutive "internal objects," which we called "fantasy objects," are thus created by the ego. This is made possible for the ego on the basis of whatever sources ("bad," or inadequate) of internal objects it has available. Bodily feelings supply a most important source of "objects" for the object-deficient ego of the schizophrenic, and this accounts for the frequency of so-called hypochondriacal preoccupations in these persons. The somatic and personal "fantasy objects," once manifest, clash with the "objective" universe of the social norm and mobilize action toward, or oftener against, the patient. Rarely, this leads to psychotherapeutic efforts. More frequently, social action leads simply to the removal and incarceration of the manifestly offending ("offensive") individual.

The physiological methods which may now be invoked, while again varied in specific technical details, share the common denominator of being destructive of the higher centers of the brain. Accordingly, the modes of action of the various shock therapies, of lobotomy, and of other destructive operations on the brain could all be said to center on interfering with the physiological function of the frontal, and to a less extent the temporal, lobe. These parts of the central nervous system are necessary for abstract thought and creative effort. They subserve the ego's growth in progressive introjections of objects and the development of the power to form and to use symbols. Similarly, they are also necessary for the compensatory effort of building up and "energizing" "fantasy objects." Destruction of parts of the brain subserving this function will, accordingly, eliminate the "symptoms" of schizophrenia insofar as these are seen in the patient's creation of "fantasy objects." Indeed, these procedures may reduce the patient to a state where he will live devoid of internal and external objects, and at the same time he might remain unoffensive in his demands upon society. The physiological treatments of schizophrenia appear quite analogous to the early medical approaches to the diabetic, who was deprived of carbohydrates and often starved of all food: By sufficiently reducing the degree of "aliveness" of the organism, we may delude ourselves into thinking that it is more "normal."

In conclusion, it may be worth while to recall the familiar fact that our concept of "health" will follow generally from our concept of "disease." If we consider schizophrenia to consist of the symptoms which society considers offensive—and this is the basis of our traditional nosology—then removal of the symptoms (irrespective of the method) will be considered "treatment." On the other hand, if we consider the deficiency of internal objects and the inability to deal with symbols as the more crucial phenomenon, then our ideas regarding diagnosis, therapy, and improvement will vary accordingly from traditional psychiatric nosology and will differ from those which advocate physical treatments for schizophrenia. The apparent paradox of

the "therapeutic" use of destroying the highest centers of the brain—which subserve the very functions that are least developed in most people (not only from a "scientific" but also simply from an evolutionary point of view)—becomes understandable by a clearheaded and explicit emphasis on our notions of "pathology."

Summary

The aim of this essay is to attempt a synthesis of psychoanalytic contributions to "schizophrenia" with certain concepts and theories of nonanalytic psychologists and philosophers bearing on the nature and function of the human use of symbols. It is suggested that there is a fundamental interdependence between the development of object relationships and of internal objects, on the one hand, and the adult ability to conceive abstractions and use symbols, on the other.

A formulation of the concept of "schizophrenia" unburdened by the medical model of "disease" and independent of whether its classic symptoms are manifest or not, is put forward. "Schizophrenia" is viewed as a particular mode of psychological organization whose most distinguishing feature lies in the schizophrenic ego's relationship to objects (people) and to symbols. The chief thesis of the essay lies in considering "schizophrenia" as a state of (relative) deficiency of internal objects in the adult. (This is not a primarily etiologically, or genetically, oriented hypothesis.) It is a corollary of this thesis that, in the "schizophrenic," symbol formation is impeded and objects which appear as symbols to the observer might be used in a concrete (nonsymbolic) manner. Further, the "schizophrenic" is needful of, and adapted for, certain types of human relationships which we designate as "model relationships." Society provides ample acceptable ("normal") opportunities for such relationships, as it does also for others. The term "schizophrenia," therefore, as used in this essay, is in no way synonymous with "illness," nor does it even provide a clue for the determination of whether a person is "healthy" or "disabled."

In conclusion, some implications of this thesis for the nature of various psychological and somatic "therapies" of schizophrenia are briefly discussed.

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Conversion of Adrenaline to Adrenolutin in Human Blood Serum

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Adrenochrome (3-hydroxy-N-methyl-5,6-dioxoindole) and adrenolutin (3,5,6-trihydroxy-1-methylindole) may be involved in the production of schizophrenia. These compounds have not been detected in blood, nor have enzyme systems been clearly demonstrated which can produce them from adrenaline. It is therefore of interest to show that the conversion can occur in blood serum.

Following Osmond and Smythies'[8] suggestion that schizophrenic patients may have within them an M substance related in structure to both mescaline and epinephrine, Hoffer, Osmond, and Smythies[5] discovered that adrenochrome, an oxidized derivative of epinephrine, induced psychological changes in humans. Hoffer and Osmond[2] postulated that the basic physiological abnormality in schizophrenia was an abnormality in the autonomic nervous system expressed chemically in the increased production of both acetylcholine and some oxidized derivative of adrenaline similar in structure to either adrenochrome or adrenolutin. Both these substances have similar properties in producing psychological changes (Hoffer[3]).

The presence of both adrenochrome and adrenolutin in human blood serum has not been demonstrated, although enzyme systems that could achieve this conversion are known (Green, Mazur, and Shorr[1]). Recently, Leach and Heath[6] demonstrated that epinephrine added to schizophrenic serum was rapidly converted to a new substance having an absorption peak at 395mμ. To a less degree the same conversion occurred in normal blood. The degree of conversion was significantly greater in schizophrenic serum than in normal serum. The conversion was accelerated by the addition of copper ions and inhibited by the addition of cyanide. They therefore believe that the enzyme is a copper-containing phenolase, similar to tyrosinase. When adrenochrome was added to serum, it was even more quickly converted to the new substance.

Adrenolutin (Lund[7]), a reduced derivative of adrenochrome, might be more stable in a reducing medium such as serum, which contains ascorbic acid, glutathione, and proteins rich in sulfhydryl groups. We have therefore added adrenolutin to serum, following in detail the procedure of Leach and Heath. The results obtained by the addition of epinephrine, adrenochrome, and adrenolutin to schizophrenic human serum are shown in the Figure. Readings were made in a Beckman DU spectrophotometer at 1 and 80 minutes.

The absorption curve obtained with adrenolutin after 1 minute is similar to the one obtained by incubating epinephrine in schizophrenic blood for 80 minutes. After 80 minutes there is little change in the curve. This suggests that the substance formed in blood serum from adrenaline is adrenolutin.

In conclusion, we have found that the enzyme which, according to Leach and Heath[6] occurs in higher concentration in

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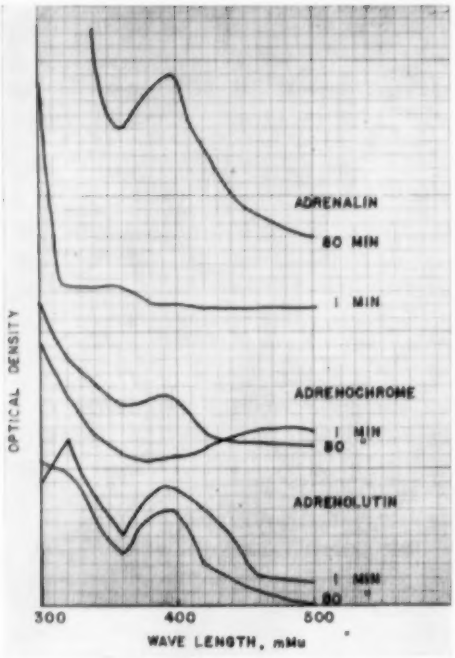
Director, Psychiatric Research, Psychiatric Services Branch, Department of Public Health, University Hospital (Dr. Hoffer). Laboratory Technician, Psychiatric Research, University Hospital (Mrs. Kenyon).



Change in specter in schizophrenic serum after addition of epinephrine, adrenochrome, and adrenolutin at 1 and 80 minutes.

schizophrenic than in normal blood, converts adrenaline to adrenolutin. This reinforces the suggestion made by our group that this oxidized derivative may play a role in the production of schizophrenia.

Psychiatric Research, University Hospital.

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Lysergic Acid Diethylamide (LSD-25) Antagonists

I. Blocking Effect of Brain Extract in the Siamese Fighting Fish; Preliminary Report

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A. Introduction

At a meeting on psychochemicals arranged by the Battelle Memorial Institute in Columbus, Ohio, on Oct. 13, 1955, Dr. A. C. K. Elliott, of the Montreal Neurological Institute, mentioned the work of Florey. He pointed out that certain dialyzed aqueous brain extracts interfered with peripheral synaptic transmission.[1] One of us (H. A. A.) asked Dr. Elliott whether he knew of the reaction of Siamese fighting fish to LSD-25 [2] and suggested that it might be of great importance to study the effect of this brain extract on the reaction of fish. Upon returning to Cold Spring Harbor, a project was set up making beef brain extracts somewhat similar to those described by Florey, with modification of the process so that perchloric acid was at times omitted and lyophilization was utilized throughout. Lyophilization avoids to a certain extent the problem connected with instability in solution. It also provides a "dry weight standard" for the crude extracts.

B. Method *

The method of observation of the blocking action was based on the criteria described by Abramson and Evans [3] for the reaction of the Siamese fighting fish to lysergic acid diethylamide (LSD-25). For the purpose of the study of brain extract, only four of these or related criteria were chosen for analysis. The main criterion utilized was the nose up-tail down position of the fish, at an angle of approximately 45 degrees or more. In addition, kink in tail and two negative criteria were employed (number of fish at top of water with nose up, and number of fish at or near bottom of container).

Observations were made every 15 minutes for 2 hours, and then for longer periods up to 17 hours. A semiquantitative appraisal of the blocking effect of brain extract was obtained from the smoothed data in Figure 1. These percentage reaction-time curves were obtained from unpublished data of Abramson, Baron, Jarvik, and Goldfarb. Photographs were made periodically with a Polaroid camera by simple fluorescent lighting. In the typical experiment reported here 10 fish were exposed to the crude brain extract for two hours before the LSD-25 was added. The highest concentration of crude brain extract used was 2 mg. per cubic centimeter. The same general results were obtained for four separate extractions.

Experimental Study

Several preliminary experiments showed that 1 mg. of lyophilized brain extract per cubic centimeter markedly inhibited the reaction of 1γ of LSD-25. However, during the period of inhibition some of the fish showed an LSD reaction which indicated that the material was not necessarily destroyed by the brain extract added but that an equilibrium of some type might take place. It was at first thought that perchloric acid used in the original procedure could have reacted with the LSD; however, dilute solutions of sodium perchlorate did not affect the fish. In order to understand the way in which the experiments were run, a typical experiment is herewith described.

Five bottles, each containing 10 fish, were set up and labeled as follows: 2 mg., 0.2 mg., 0.02 mg.,

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From the Biological Laboratory, Cold Spring Harbor, Long Island, N. Y.

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* The fish are killed if the heating procedure of Florey is followed.

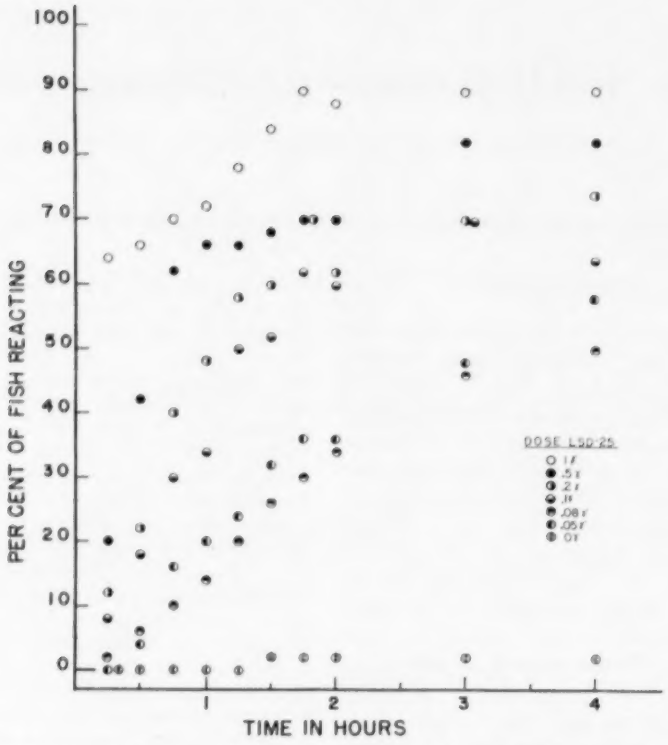


Fig. 1.—Reaction-time curves for Siamese fighting fish, with different concentrations of LSD-25 per cubic centimeter in the water. Unpublished data of Abramson, Baron, Jarvik, and Goldfarb.

H_2O, and LSD-25 (Figs. 2 through 15). The bottle labeled 2 mg. represents 2 mg. of crude brain extract per cubic centimeter; 0.2 mg. represents 0.2 mg. of crude brain extract per cubic centimeter; 0.02 mg. represents 0.02 mg. of crude brain extract per cubic centimeter; H_2O is the water control, and the bottle labeled LSD-25 is that bottle which will later contain 2γ per cubic centimeter of LSD-25 only (no brain extract). There was no definite effect that could be readily observed in the fish due to the brain extract itself, although the bottle containing 0.2 mg. of crude brain extract per cubic centimeter showed the fish to be near the surface of the water oftener than the lower and higher concentrations. Two hours after the brain extract acted, 2γ of LSD-25 per cubic centimeter was added to all bottles except the H_2O control. The experiment can best be followed by studying Figures 2 through 15.

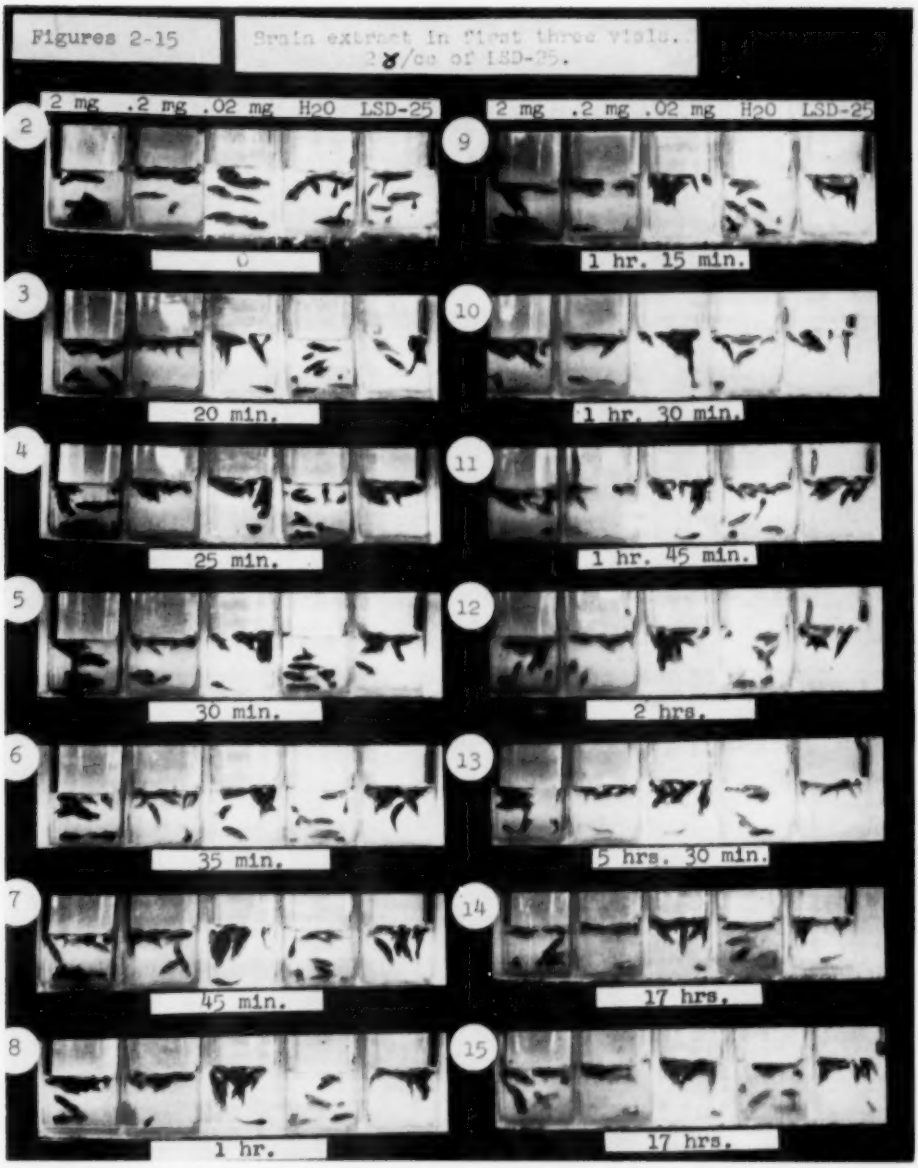
Fig. 2.—This picture was taken immediately after 2γ of LSD-25 per cubic centimeter had been added to all bottles except the H_2O control. The fish are seen swimming at random in all bottles except the one labeled 0.2 mg., in which most of the fish were near the top, but with tail up.

Fig. 3.—Twenty minutes after LSD-25 was added the fish are seen swimming at random in bottles labeled 2 mg. and H_2O. In bottle labeled 0.02 mg., the fish are beginning to show LSD-25 behavior, that is, proximity to top of water and the nose up-tail down position.

Fig. 4.—Twenty-five minutes after LSD-25 was added the fish in bottles labeled 2 mg. and H_2O are seen swimming at random. All but one fish in bottle labeled 0.02 mg. show typical LSD-25 positions. In bottle labeled LSD-25 all fish show LSD-25 behavior.

Fig. 5.—Thirty minutes after LSD-25 was added the fish in bottles labeled 2 mg. and H_2O are still swimming at random. In bottle labeled 0.02 mg. all but one fish show the LSD effects, that is, the nose up-tail down position. In bottle labeled LSD-25, all but one fish is at the top of the water and nose up-tail down.

Fig. 6.—Thirty-five minutes after LSD-25 was added, all fish are swimming at random in bottles



Figs. 2-15.—Effect of crude brain extract on the LSD-25 reaction in the Siamese fighting fish.

labeled 2 mg. and H_2O. In bottle labeled 0.02 mg. 8 out of 10 fish are nose up-tail down. In the bottle labeled LSD-25, all fish are nose up-tail down.

Fig. 7.—Forty-five minutes after LSD-25 was added, six fish in bottle labeled 2 mg. are near the top, and two fish appear to be in the nose up-tail down position. The typical LSD-25 reaction is now beautifully illustrated in the 0.02 mg. bottle and in the LSD-25 control. One fish is dead in the 0.02 mg. bottle.

Fig. 8.—One hour after LSD-25 was added, 8 out of 10 fish in the 2 mg. bottle are swimming near the top, but not all in the nose up-tail down

position. All fish in the 0.02 mg. bottle are nose up-tail down. In the LSD-25 control all fish are clustered at the top of the water, several in the nose up-tail down position. The water controls are still normal.

A similar study of Figures 9 through 15 shows the persistent effects of LSD-25 except in the presence of considerable brain extract. The H_2O controls still show the fish to be normal in appearance and swimming at random. The higher concentration of brain extract in the 2 mg. bottle shows the gradual development of the LSD-25 reaction, but never the full effect, as exemplified in the 0.02 mg. and LSD-25 bottles. About half of the fish show an LSD-25 reaction in the 2 mg. bottle. In the 0.2 mg. bottle the fish were still clustered at the top of the water.

The four criteria of behavior described under "Method" were used to obtain the data shown in the accompanying Table. This Table illustrates the general nature of the bioassay method currently employed. It is to be noted that until LSD-25 was added

Effect of Brain Extract on the LSD-25 Reaction

in Siamese Fighting Fish

Time Hrs.	2 mg/cc Brain Extract				0.2 mg/cc Brain Extract				0.02 mg/cc Brain Extract			
	1*	2*	3*	4*	1*	2*	3*	4*	1*	2*	3*	4*
0	0	0	2	1	0	0	1	1	0	0	0	1
:15	0	0	1	2	0	0	1	1	0	0	2	0
:30	0	0	0	2	0	0	2	0	0	0	0	4
:45	0	0	0	0	0	0	5	0	0	0	1	3
1:00	0	0	4	0	0	0	9	0	0	0	2	4
1:15	0	0	1	2	0	0	9	0	0	0	0	3
1:30	0	0	1	3	0	0	8	2	0	0	0	4
1:45	0	0	1	3	0	0	8	1	0	0	0	2
2:00	0	0	2	4	0	0	6	0	0	0	1	4
	2 γ/cc LSD-25 added				2 γ/cc LSD-25 added				2 γ/cc LSD-25 added			
:15	0	0	5	3	3	3	2	0	10	10	0	0
:30	1	0	3	4	10	10	0	0	10	10	0	0
:45	1	0.	3	4	9	10	0	0	9†	9	0	1
1:00	4	4	1	2	8†	9	0	2	9	10	0	1
1:15	4	4	3	2	9	10	0	1	10	10	0	0
1:30	6	6	1	2	9	10	0	1	9	10	0	1
1:45	5	6	3	2	9	10	0	1	9	10	0	1
2:00	5	7	2	1	8	10	0	1	9	10	0	1

	Water Control				LSD-25 Control			
	1*	2*	3*	4*	1*	2*	3*	4*
0	0	0	2	1	0	0	2	1
:15	0	0	0	1	0	0	0	2
:30	0	0	0	0	0	0	1	2
:45	0	0	3	2	0	0	2	1
1:00	0	0	3	2	0	0	3	3
1:15	0	0	2	3	0	0	2	4
1:30	0	0	2	3	0	0	4	2
1:45	0	0	1	5	0	0	4	3
2:00	0	0	2	2	0	0	2	3
	----------				2 γ/cc LSD-25 added			
:15	0	0	2	2	10	10	0	0
:30	0	0	0	3	10	10	0	0
:45	0	0	3	4	10	10	0	0
1:00	0	0	2	4	10	10	0	0
1:15	0	0	3	2	10	10	0	0
1:30	0	0	6	3	10	10	0	0
1:45	0	0	4	2	10	10	0	0
2:00	0	0	4	1	10	10	0	0

* 1- Nose up--tail down
2- Kink in tail
3- Top of water--tail up
4- Bottom of container

† Note: One fish dead.

none of the fish showed the nose up-tail down position except as a normal movement. Fifteen minutes after the LSD was added to the five vessels all the fish in the LSD-25 control showed the nose up-tail down position and continued to do so throughout the experiment. Similar results were essentially obtained in the bottle containing 0.02 mg. per cubic centimeter of crude brain extract. In the 0.2 mg. bottle the fish were essentially in nose up-tail down position and at the top of the water 30 minutes after LSD was added, and remained so throughout the experiment. In the bottle containing 2 mg. of brain extract per cubic centimeter, however, there is a definite reaction lag, since at the end of 45 minutes only one fish showed the nose up-tail down position. At no time during the subsequent period of observation were all

Fig. 16.—Negative effect of serotonin on the LSD-25 reaction in the Siamese fighting fish.

of the fish in the 2 mg. concentration nose up-tail down.

Using the curves in Figure 1 to determine the effective concentration of LSD-25, it follows that the fish in the bottle containing 2 mg. of brain extract per cubic centimeter acted as though approximately 0.2γ of LSD-25 per cubic centimeter were present. In other words, the brain extract blocked the appearance of the LSD effect. When the LSD effect finally did make its appearance, the effect resembled that of a much weaker solution of LSD than was actually added. This method confirms the observations made photographically (Figs. 2 through 15). The initial excitement produced by LSD was not observed in the presence of 2 mg. per cubic centimeter.

C. Action of Serotonin, Amino Acids, and Histamine

The question naturally arose: Is the serotonin present in the brain extract responsible for the action of the brain extract? Figure 16 illustrates the effect of serotonin on the LSD-25 reaction. Two hours after the fish were in serotonin LSD-25 was added. One thousand times as much serotonin was added as was LSD-25. Inspection of Figure 16 reveals that serotonin does not block the LSD-25 reaction.

Negative results were also obtained with histamine. In studying the amino acids, three bottles containing 2 mg. per cubic centimeter of each of the amino acids in 100 cc. of water was used, with five fish in each bottle. Two micrograms of LSD-25 per cubic centimeter was added after 10 minutes to the first bottle, and after 2 hours to the second bottle. The third bottle was the control (no LSD-25). An LSD control (LSD added after 10 minutes to a bottle containing five fish and 100 cc. of H_2O) and a water control were also run for each series. The pH of the solutions was regulated so that the solutions were approximately pH 6. The bottles were kept at 80 F in a water bath.

Negative results were found with γ-aminobutyric acid, as well as with the following amino acids: l-hydroxyproline; l-serine; 3,5-diiodo-l-tyrosine; DL-α-aminobutyric acid; DL-cysteine hydrochloride; l-lysine hydrochloride; DL-methionine; l-tyrosine; DL-valine; DL-tryptophan; l-leucine; DL-phenylalanine; acetyl glycine; l-arginine hydrochloride; DL-threonine; l-histidine hydrochloride; l-glutamic aicd; l-valine; acetyl-DL-phenylaline; glycine; and l-proline.

There was possibly slight blocking by l-histidine, where all the fish did not react to LSD immediately.

D. Comment

Lack of material (due to the difficulty of preparing the crude brain extract in quantity) has prevented determining where the blocking substance acts or what it is. Conceivably, it may act in several places: (1) outside the fish, forming a loose compound with LSD-25; (2) at the gill membrane, or (3) inside the fish itself, as a pharmacologic inhibitor in the nature of an antimetabolite or pharmacologic antagonist. We believe the action to be very different, indeed, from the depressant effect of large doses of chlorpromazine on the LSD reaction in man, since the brain extract itself in the concentrations employed has very little effect on the normal activity of the fish. With our present experimental technique no effect of the brain extract itself has been observed, although slow colored motion pictures might depict changes due to the chemicals in the brain extract itself. The data indicate that some type of equilibrium is set up where the inhibitor action is dependent on the concentration of the LSD-blocking substance present in the liquid. Future experiments are being designed on mammals and on man to estimate whether the brain extract inhibits the LSD reaction as it does in the fish. In view of the small amount of material obtained from beef brain, our present methodology is being scrutinized in an effort to obtain more of the inhibitory substances from beef brain or from other tissues and other animals. Whether the LSD-blocking substance is

similar to Florey's synaptic inhibitor remains to be determined.

E. Summary

Crude brain extract up to concentrations of 2 mg. per cubic centimeter of the mixture does not essentially change the behavior of the Siamese fighting fish.

If the fish are allowed to remain in contact with this concentration of crude brain extract for two hours, addition of LSD-25 (2γ per cubic centimeter) does not have its usual effect.

Whereas 0.02 and 0.2 mg. of crude brain extract per cubic centimeter have a minor effect on the LSD reaction, 2 mg. of crude brain extract per cubic centimeter blocks the LSD reaction. The LSD reaction observed corresponds to a concentration of 0.2γ of LSD per cubic centimeter.

If the blocking effect occurs within the fish, this is apparently the first time that blocking action (not a symptomatic depressant) of behavior changes engendered by LSD has been produced by a biologically derived substance.

133 E. 58th St. (22).

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News and Comment

ANNOUNCEMENTS

The American Board of Psychiatry and Neurology, Inc.—The following candidates were certified by the American Board of Psychiatry and Neurology, Inc., at a meeting of the Board in New York, Dec. 10 and 11, 1956. Supplementary certification is indicated by an asterisk(*) preceding the name.

PSYCHIATRY

Adam, John Charles, Central Islip, N. Y.
Adams, Hugh, Cooperstown, N. Y.
Amargos, Gerardo, M., Milton, Mass.

Baden, David D., New York
Band, Raymond I., Baltimore
Barash, Bernard, Pittsburgh
Bash, Nicholas P., Philadelphia
Bell, James Milton, Topeka, Kan.
Bernath, Andrew K., New York
Boaz, Willard Denton, Cleveland
Bowser, Lawrence Pendleton, Waltham, Mass.
Boyle, Desmond G., San Diego, Calif.
Brayboy, Thomas Lee, White Plains, N. Y.

Camp, William P., Norristown, Pa.
Chafetz, Morris E., Newton Centre, Mass.
Chodosh, H. Louis, Paterson, N. J.
Coblentz, Adrien L., New York
Coleman, Louise J., New York
Colett, Ilse Vivien, Fresno, Calif.
Cook, John Alfred, New York
Coolidge, John C., Cambridge, Mass.
Coppola, Ralph J., Pittsburgh
Crandall, Richard Andrews, Jr., Norristown, Pa.
Cowen, Joseph Robert, Towson, Md.
Crawshaw, Ralph S., Topeka, Kans.
* Cullen, Chester F., Hartford, Conn.

d'Amato, Gabriel, Savannah, Ga.
Dasher, Samuel P., New York
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Doyle, Thomas Leonard, Jr., Arlington, Va.

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Edelman, Richard Joseph, Syracuse, N. Y.
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Feldman, Joseph H., New York
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Friedman, Cyrus R., Pittsfield, Mass.
Friedman, Marcia Laura Gordon, Miami, Fla.
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Gambill, John Randolph, Norwich, Conn.
Gardner, Edward B., New York
Gianakon, Harry G., Kansas City, Kan.
Gifford, Sanford R., Jr., Boston
Gillman, Arthur E., Woodmere, N. Y.
Goldberg, Martin, Philadelphia
Goldstein, Herbert S., Bayside, N. Y.
Greenlee, Robert L., Fort Wayne, Ind.
Greenleigh, Lawrence, Beverly Hills, Calif.
Guttmann, Oskar, New York

Haley, Argus B., Buffalo
Hall, Laurence Bartlett, Norristown, Pa.
Holter, Frank Robert, Philadelphia
Honig, Emanuel M., Beverly Hills, Calif.
Horan, John S., Sepulveda, Calif.
Horecker, Leonard, Anna, Ill.
Howard, Bede F., Coatesville, Pa.

Jackamets, Michael, West Brentwood, N. Y.
Jackel, Merl M., New York
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Johnson, James A., Milwaukee
Jordan, Patricia, Chicago

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Katz, Henry E., Buffalo
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Shevin, Frederick Franklin, New York
Shoemaker, Thomas E., II, Belle Mead, N. J.
Smith, Kathleen, St. Louis
Steinbach, Richard A., Washington, D. C.
Stern, George Marvin, Hartford, Conn.
Stuen, Marcus R., Woolley, Wash.
Sullivan, Albert W., Rochester, N. Y.
Suslick, Alvin, Chicago

Targownik, Karl K., Topeka, Kan.
Teichner, Victor Jerome, New York
Therman, Per-Olof G., Philadelphia

Unger, William L., Beverly Hills, Calif.

Vecchione, Felix S., Haydenville, Mass.

Wasser, David Alexander, Iowa City
Waterman, Roger S., Baltimore
Watson, Andrew S., Philadelphia
Watson, E. Jane, Rochester, Minn.
Welz, Werner K. R., Drexel Hill, Pa.
Willig, Wanda, New York
Wood, Edwin Charles, West Haven, Conn.

Zell, John Richard, Whitefish Bay, Wis.

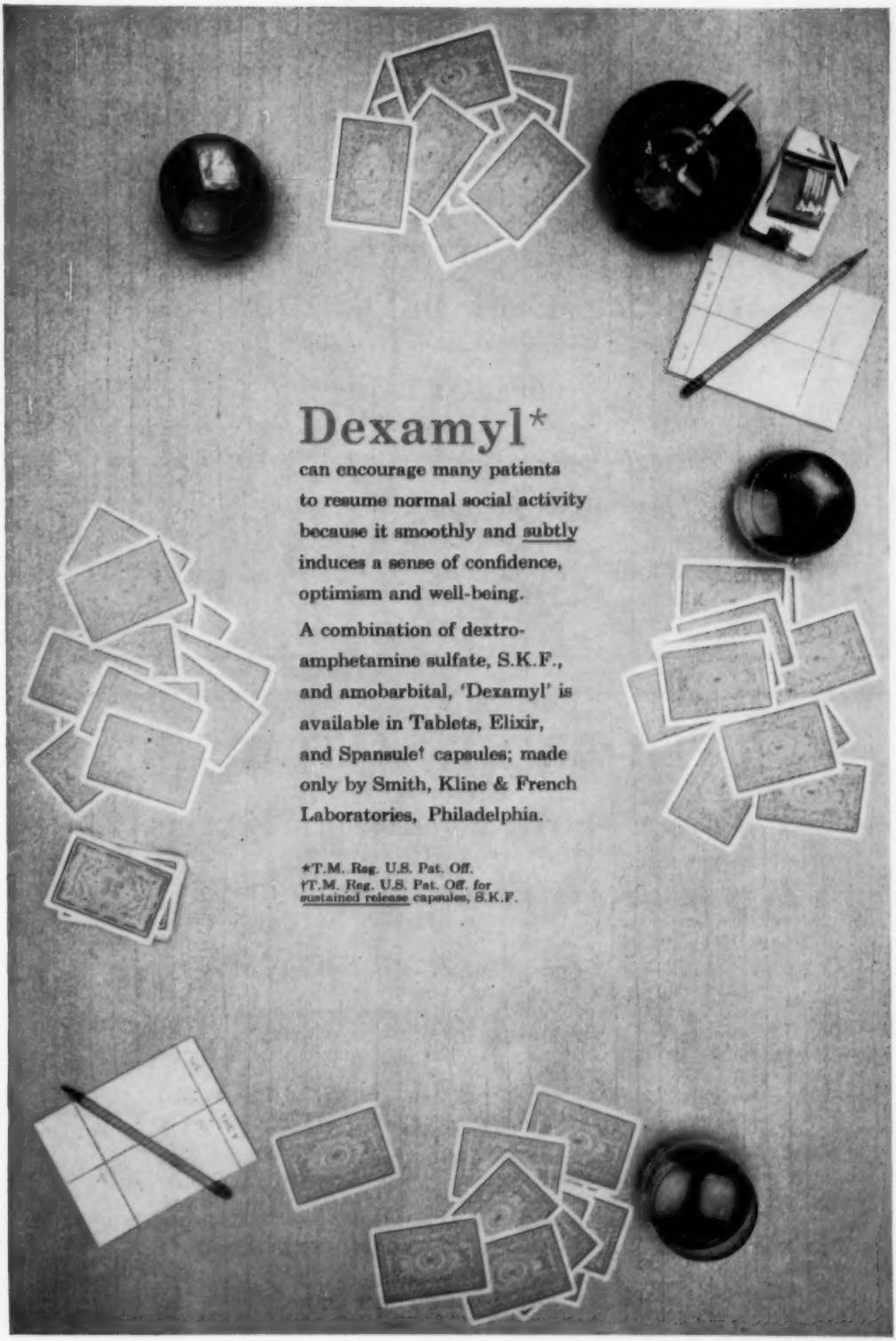
Books

BOOK REVIEWS

Basic Readings on the MMPI in Psychology and Medicine. Edited by George S. Welsh and W. Grant Dahlstrom. Price, $8.75. Pp. 656. University of Minnesota Press, 10 Nicholson Hall, Minneapolis 14, 1956.

The Minnesota Multiphasic Inventory (MMPI) attempts to provide an objective appraisal of some of the major personality characteristics of particular concern to persons working in the area of psychopathology. In the fifteen years since it was first introduced, an astonishing total of almost 700 publications has appeared inquiring into and demonstrating the potential of this test both as a research instrument and as a practical clinical aid.

The present volume consists mainly of a compilation of 66 of these articles, constituting the principal research and clinical developments in the use of the MMPI. It is organized into 10 sections, devoted to theory and construction of the test, coding procedures, new scales, profile analysis, diagnostic patterns, and applications of the technique to several important areas in psychology and medicine. The editors have had to abridge all papers so as to minimize repetitiveness. Yet each is still a unit that is topical and complete in its own right. Although aimed primarily at the new student, this work will also remain a valuable source book for practicing psychologists and investigators for some time to come.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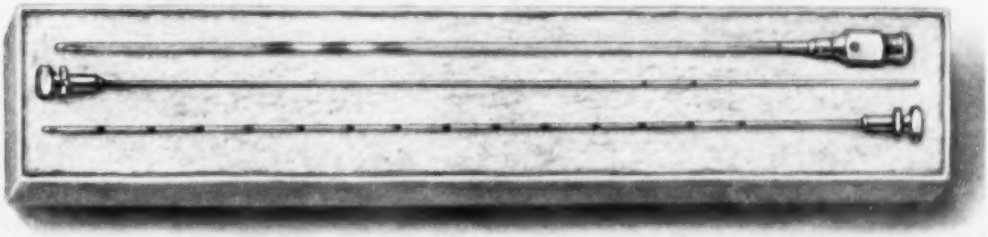

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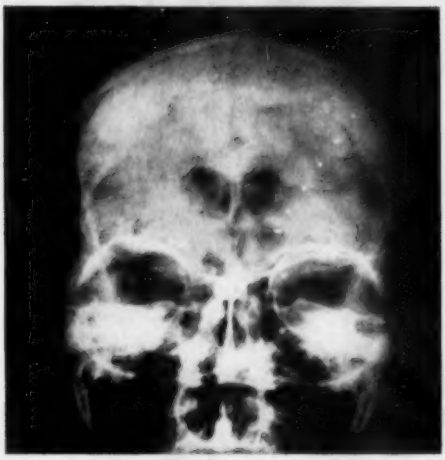

X-ray to determine position of cannula. Note radiopaque markings of stylet.

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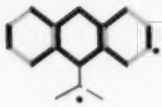
2. A stainless steel stylet for insertion of the cannula.

3. A nylon stylet with radiopaque markings at 1 cm. intervals for indwelling use.

References

*Cooper, I. S.: Chemopallidectomy: An Investigation Technique in Geriatric Parkinsonians, Science 121: 217-218 Feb. 1955.

*Cooper, I. S.: The Neurosurgical Alleviation of Parkinsonism. Springfield, Ill.: Charles C. Thomas, Publisher. 1956.



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1. Rockmore, L.; Shatin, L., and Funk, I.C.: Psychiat. Quart. *30*:189 (April) 1956.

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.